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UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

NADIA SHASH and AMJAD KHAN Individually and On Behalf of All Others Similarly Situated, Plaintiffs, v. BIOGEN INC., MICHEL VOUNATSOS, ALFRED W. SANDROCK, JR., and SAMANTHA BUDD-HAEBERLEIN, Defendants.	**CASE No.: 1:21-cv-10479-IT** **SECOND AMENDED CLASS ACTION COMPLAINT FOR VIOLATION OF THE FEDERAL SECURITIES LAWS**

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Lead Plaintiff Nadia Shash and Named Plaintiff Amjad Khan, individually and on behalf of all other persons similarly situated, by their undersigned attorneys, for their complaint against Defendants (defined below), allege the following based upon personal knowledge as to themselves and their own acts, and information and belief as to all other matters.

I. INTRODUCTION[1]

1. This is a federal securities class action on behalf of all persons or entities who purchased or otherwise acquired publicly traded Biogen securities between October 22, 2019 and November 6, 2020, inclusive ("Class Period"), and were damaged upon the revelation of the alleged corrective disclosures. Plaintiffs seek to recover damages caused by Defendants' violations of the federal securities laws under the Securities Exchange Act of 1934 ("Exchange Act").[2]

2. Defendants misled investors about the results of clinical trials on what would be the most profitable treatment ever approved by the FDA, while concealing the data that proved the statements were misleading. Defendants made their false statements at least recklessly. Their statements were clear and deliberate, and Defendants repeated them for almost a year while concealing the data that showed the statements were obviously false. They misled investors about issues Defendants themselves admitted were critical. And Defendants made their false statements after spending six months personally overseeing an exhaustive analysis of the clinical trial data. The deficiencies Defendants' statements concealed caused an FDA advisory panel to vote against

[1] Unless otherwise noted, all emphases are added.

[2] Excluded from the class are Defendants, all officers and directors of Biogen, their immediate family members and any entity over which an excluded person exercises control or owns more than 10%.

aducanumab's approval 10-0. Biogen's stock price fell 28.2% in one day, costing investors more than $10 billion.

3. Defendants staked Biogen's future on an Alzheimer's disease treatment, aducanumab. Aducanumab removes amyloid plaque, which is present in the brains of patients suffering from Alzheimer's disease. Removing plaque, Biogen hopes, slows disease progression. If it obtained FDA approval, aducanumab would become the first Alzheimer's disease therapy that does more than treat symptoms.

4. Aducanumab's Phase III clinical trials consisted of two identically designed international studies, Study 301 (also known as ENGAGE) and Study 302 (EMERGE), each with about 1,600 patients. Each study was divided into three arms of equal size: placebo, low dose and high dose. The studies' primary endpoint was the change in CDR-SB scores, a measure of cognitive and functional decline, after 18 months. Aducanumab was not expected to improve (lower) CDR-SB scores, or even maintain cognitive abilities, but only to slow cognitive and functional decline.

5. In March 2019, Biogen halted aducanumab's clinical trials because, based on a pre-specified intermediate "futility" analysis, aducanumab had failed to show efficacy and it was improbable that the clinical trials would reach their endpoints if continued to conclusion. Defendants had lost their bet.

6. Biogen's stock price collapsed. It faced a bleak future. Its sales were declining, and its patents were either expiring or under legal challenge. Defendants' personal futures looked bleak, too: shepherding Biogen through its slow decline to dissolution is hardly an executive's dream job.

7. With no plausible replacement, Defendants sought to resuscitate aducanumab. Using additional patient data collected between when the futility database was locked and when futility was declared, Biogen was able to find Study 302 just barely statistically significant on its primary endpoint. Defendants then claimed Study 302 succeeded.

8. But they needed something more. Study 301 failed. In fact, in Study 301, patients on high dose aducanumab did worse than placebo. When the FDA receives an application with one positive and one negative clinical study, it will, at best, ask the sponsor to run another trial. Because the measure of aducanumab's effectiveness is whether it produces results after 18 months and recruiting a sufficient number of patients takes time, another trial would take 3 years or more. Defendants sought to avoid that fate.

9. Defendants tasked 49 Biogen statisticians with sifting through Study 301 data to find any pretext to claim that the study might support aducanumab's approval, under the close supervision of Defendants Samantha Budd-Haeberlein and Alfred Sandrock. Eventually, they did.

10. Defendants had amended the trials' protocol in March 2017. The amendment altered the maximum possible dose for patients who carried a gene that predisposed them to Alzheimer's Disease (ApoE ε4, or APOE4 herein), who made up two thirds of the study population. Before the amendment, APOE4 carriers (Carriers, or APOE4 Carriers) who were placed in the trials' high dose arm received only 6mg/kg because APOE4 also predisposes them to an aducanumab side effect, ARIA.[3] After the amendment, they received the full 10mg/kg high dose.

[3] ARIA is an acronym for Amyloid Related Imaging Abnormalities thought to represent vasogenic edema and cerebral micro-hemorrhages. ARIA were first reported in 2009 in clinical trials of bapineuzumab1,2 and have since been associated with other investigational anti-Amyloid Beta monoclonal antibodies for the treatment of Alzheimer's disease.

11. Since Study 301 started before Study 302, more Carriers in Study 302 received the maximum 10 mg/kg dose of aducanumab for a longer portion of their treatment, which Defendants told investors accounted for the studies' different outcomes. Defendants claimed, too, that throughout aducanumab's clinical trials, patients had achieved clinical outcomes that were related to the dose of aducanumab they received, called a dose-response relationship. And they claimed that the high dose of 10mg/kg sufficed to generate positive results. Yet the data Defendants concealed showed this explanation was objectively false:

- In Study 302, Carriers who received 6mg/kg achieved better outcomes than those who received 10mg/kg;
- The number of 10mg/kg doses had no impact in Study 302; and
- APOE4 non-carriers (Non-Carriers or APOE4 Non-Carriers), who should have received the greatest benefit of all because they always received the 10mg/kg dose and their treatment was never interrupted by side effects, saw no benefit in either Study 301 or 302.

12. More, Defendants claimed, aducanumab had ***worked as intended***. Aducanumab unquestionably removes amyloid plaque. But whether removing plaque leads to better clinical outcomes is, as one expert put it, the "million-dollar question", and Defendants acknowledged the question was "very important". Defendants claimed that in aducanumab's Phase III trials, removing plaque had ***actually caused*** better clinical outcomes for patients in aducanumab's clinical trials. Here, they paused to note, less plaque had been removed from patients in Study 301 than in Study 302 – which explains why Study 301 was a negative study.[4]

[4] Defendants also falsely denied that there were meaningful regional or demographic differences in treatment outcomes, while misleadingly claiming that positive results on secondary endpoints

13. Defendants' statement that removal of plaque correlated with and even caused better clinical outcomes was outright false. There was no correlation. In fact, in Study 302, plaque removal was associated with *worse* clinical outcomes.

14. Defendants' statements that patients who received more 10mg/kg doses saw better clinical outcomes were misleading. In Study 302, Carriers who received 6mg/kg performed slightly better than those who received 10mg/kg. The number of 10mg/kg doses, which Defendants said was critical in Study 301, had no impact in Study 302. And Non-Carriers, who should have received the greatest benefit of all because they always received the 10mg/kg dose and their treatment was never interrupted by side effects, saw no benefit in either Study 301 or 302. As one doctor observed, the Study 302 data Defendants concealed showed that their claims about Study 301 "don't make any sense at all."

15. The truth Defendants' statements concealed is that a certain sub-group of patients in Study 301 had performed better than others, not because aducanumab had any different effect, but because through random chance, some arbitrary group of patients will always achieve better results than others. When Biogen's 49 statisticians scrutinized the study data they were bound to identify a sub-group that had an adequate response to the test drug. Because they withheld the data that proved their statements false, Defendants' false narrative convinced investors and even world-renowned Alzheimer's disease specialists that Study 301 was at least explicable, and that at best it even supported Study 302 by showing that aducanumab was effective at the 10mg/kg dose.

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buttressed the case for aducanumab without disclosing that the result showed it's because they all measured the same thing.

16. On November 6, 2020, Defendants were to appear before an FDA advisory committee ("Advisory Committee"), a group of experts who hold a public hearing to discuss the merits of product applications and advise the FDA on specific questions it poses. The Advisory Committee would determine whether to recommend that the FDA approve aducanumab. The briefing materials for the meeting were published on November 4. They included, but buried, a report by Tristan Massie, PhD, the FDA's statistical reviewer on aducanumab's application. Massie relied on the raw data denied the public and researchers. He ran the analyses and presented the data Biogen had concealed from investors. And his report showed that Defendants' statements had been false: there was no correlation between removal of amyloid plaque and clinical outcomes; there was no difference between patients who received 6mg/kg or 10mg/kg in Study 302; a full third of patients who always received the full number of 10mg/kg doses, the APOE4 non-carriers, saw no benefit in either Study; and there was no correlation between removal of amyloid plaque and clinical outcomes.

17. Biogen's stock price fell by 7.5% on November 5 as investors digested the complex report.

18. The Advisory Committee voted 10-0 against approving aducanumab. Their decision was based principally on the analyses Massie ran in his report showing that aducanumab provided no clinical benefit to Alzheimer's patients, with which they agreed.

19. Biogen's stock was halted all day on November 6 because of the Advisory Committee meeting. When it resumed trading on November 9, the price of Biogen's stock fell from its previous close of $328.90 to fall to $236.26, down 28.2%.

20. Then, on June 7, 2021, the FDA approved aducanumab.

21. Flash back to two months after the futility declaration. In May 2019, Defendant Sandrock and an old colleague, Dr. Billy Dunn, were both attending the American Academy of Neurology 2019 Annual Meeting in Philadelphia. Dunn was more than an old colleague of Sandrock's. He also led the FDA's Office of Neurology, the frontline office for aducanumab's approval. At that Annual Meeting, Sandrock arranged a secret, off-the-books meeting with Dunn. At their secret meeting, Sandrock persuaded Dunn to move forward with aducanumab's FDA approval. Then in June 2019, with scarcely any further analysis, Dunn's office determined that it would find a way to approve aducanumab notwithstanding the failed clinical trial. Dunn's office and Defendants then formed a joint task force to develop a fig leaf justification to approve aducanumab. Biogen and Dunn's office communicated nearly daily as they ran joint analyses. They even plotted, ***together***, how they would push aducanumab through approval. As one Biogen employee put it, "[i]t was clear that Billy Dunn was an ally, so the job for Biogen became figuring out how to support his efforts within the FDA."

22. The disastrous November 2020 Advisory Committee meeting did not end Dunn's quest. In March and April 2021, Dunn and his colleagues appeared before a standing committee made up of the FDA's most senior staff to push for approval of aducanumab. They argued, once again, that the clinical trial data supported approval. The FDA's committee shot down Dunn with the "vast majority" of members voting against approval.

23. At the meeting, the head of the FDA's oncology office off-handedly raised a possibility: approval based on a surrogate endpoint that is not itself of clinical interest but which is generally believed to be correlated with clinically important results. Surrogate endpoints are commonly used in oncology, and also in vaccines. The oncologist wondered whether aducanumab might be approved based on its effect on amyloid plaque.

24. Dunn had previously told the Advisory Committee the FDA was not considering approving aducanumab based on its impact on amyloid plaque (a surrogate endpoint), but the Advisory Committee and internal FDA votes foreclosed regular approval. He and his colleagues had not even seriously raised the possibility at the March and April 2021 meetings. So, with only months to spare before a June 7, 2021 deadline to approve or reject aducanumab, Dunn, his colleagues, and Defendants took the only path still available to them.

25. Dunn's colleague convened a meeting to determine whether to approve aducanumab because it reduced amyloid plaque. They sought no advice. Instead, they invited the heads of the FDA's oncology and vaccine offices, neither of which had anything to do with Alzheimer's disease. To ensure a successful vote, they gave these office heads a vote. And thus aducanumab, which promises to cost the public fisc tens of billions of dollars per year, came to be approved: based on a few months' consideration, after multiple expert bodies had panned the application, supported by the votes of the heads of a cancer and a vaccine office.

26. The decision caused an immediate uproar. And so, three weeks later, did the revelation by an investigative report of Sandrock and Dunn's secret meeting and other eyebrow-raising contacts.

27. Three of nine permanent advisory committee members resigned, with one calling approval "probably the worst drug approval decision in recent U.S. history."

28. The American Neurological Association published a statement that aducanumab should not have been approved.

29. A respected third-party advisory panel with influence over third-party payor decisions found that there is no evidence aducanumab has any benefit whatsoever.

30. Mt. Sinai Health System, the Cleveland Clinic, and a network that operates 52 hospitals and more than 1,000 outpatient clinics announced they would not administer aducanumab.

31. Senator Joe Manchin called for the FDA's acting commissioner's replacement over the aducanumab approval decision.

32. Two House Committees launched investigations into Biogen's relations with the FDA.

33. The longest-serving Secretary of Health and Human Services called for the Department of Health and Human Service's Office of the Inspector General to investigate contacts between high-level FDA staff and Biogen. Days later, the FDA's acting commissioner joined the request.

34. A July 2021 survey of neurologists reported that 80% had lost confidence in the FDA in the previous year.

35. Investors bought Biogen's stock after Defendants made claims about aducanumab's clinical trials that simply weren't true. They lost money when those claims were shown to be false. That Defendants could count on Dunn to do his utmost to push aducanumab through to approval no matter what the data showed is not a defense to securities fraud.

II. JURISDICTION AND VENUE

36. The claims asserted herein arise under §§10(b) and 20(a) of the Exchange Act (15 U.S.C. § 78j(b) and §78t(a)) and Rule 10b-5 promulgated thereunder (17 C.F.R. § 240.10b-5).

37. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. § 1331 and §27 of the Exchange Act.

38. Venue is proper in this judicial district pursuant to §27 of the Exchange Act (15 U.S.C. § 78aa) and 28 U.S.C. § 1391(b) as the alleged misstatements entered and the subsequent damages took place in this judicial district.

39. In connection with the acts, conduct and other wrongs alleged in this Complaint, Defendants, directly or indirectly, used the means and instrumentalities of interstate commerce, including but not limited to, the United States mail, interstate telephone communications and the facilities of the national securities exchange.

III. PARTIES

40. Lead Plaintiff Nadia Shash, as set forth in her PSLRA Certification which was previously filed and is incorporated by reference, purchased Biogen securities at artificially inflated prices during the Class Period and was damaged thereby.

41. Named Plaintiff Amjad Khan, as set forth in his PSLRA Certification which was previously filed and is incorporated by reference, purchased Biogen securities at artificially inflated prices during the Class Period and was damaged thereby.

42. Defendant Biogen Inc. is a Delaware company headquartered in Cambridge, Massachusetts. Biogen discovers, develops, and manufactures products to treat neurological and neurodegenerative diseases, as well as autoimmune and hematologic disorders. Biogen's principal product is aducanumab, which during the Class Period was an investigational biologic studied for the treatment of Alzheimer's disease. Biogen's securities trade on the NASDAQ Exchange under the ticker symbol "BIIB".

43. Defendant Michel Vounatsos has served as the Company's CEO and as a Director since January 2017.

44. Defendant Alfred W. Sandrock, Jr., has served as Biogen's Chief Medical Officer since October 2015. He served as Executive Vice President – Neurology Discovery and Development from October 2015 to October 2019, when he was promoted to the position of Executive Vice President – Research & Development.

45. Defendant Samantha Budd-Haeberlein served as Biogen's Vice President of Clinical Development from February 2015 through March 2020 and has served since then as its Senior Vice President – Head of Neurodegeneration Development Unit.

46. Defendants Vounatsos, Sandrock, and Budd-Haeberlein are the "Individual Defendants."

47. The Company is liable for the acts of the Individual Defendants and its employees under the doctrine of *respondeat superior* and common law principles of agency because all of the wrongful acts complained of herein were carried out within the scope of their employment.

48. The scienter of the Individual Defendants and other employees and agents of the Company is similarly imputed to the Company under *respondeat superior* and agency principles.

49. The Company and the Individual Defendants are referred to herein, collectively, as the "Defendants."

IV. CERTAIN IMPORTANT EVENTS

50. Defendants and the FDA held at least seven meetings concerning aducanumab that are relevant to this Complaint, which are identified here:

Meeting	Attendees (among others)
December 16, 2014 Type B meeting ("December 2014 Meeting")	Dunn
Mid-May 2019 off-the-books meeting in Philadelphia ("Off-the-Books Meeting")	Dunn, Defendant Sandrock

June 14, 2019 Type C meeting ("June 2019 Meeting")	Dunn, Defendants Sandrock and Budd-Haeberlein
October 21, 2019 Type C meeting ("October 2019 Meeting")	Dunn, Defendants Sandrock and Budd-Haeberlein
February 26, 2020 Type C meeting ("February 2020 Meeting")	Dunn, Defendant Budd-Haeberlein
June 17, 2020 Type C meeting ("June 2020 Meeting")	Dunn, Defendant Budd-Haeberlein
November 6, 2020 Advisory Committee Meeting ("Advisory Committee Meeting")	Dunn, Defendant Budd-Haeberlein

51. The Defendants made numerous presentations to investors in which they made false statements, which are identified here:

a. October 22, 2019 call to discuss Biogen's Q3 2019 earnings and aducanumab's revival ("Q3 2019 Call");

b. Michel Vounatsos October 23, 2019 MSNBC interview ("October 2019 MSNBC Interview");

c. December 5, 2019 presentation at the Clinical trials on Alzheimer's Disease conference to present aducanumab's Phase III topline results ("December 2019 Results Presentation");

d. December 5, 2019 Q&A call to discuss aducanumab's Phase III topline results ("December 2019 Q&A");

e. January 30, 2020 call to discuss Biogen's Q4 2019 earnings ("Q4 2019 Call");

f. April 2, 2020 encore presentation of aducanumab Phase III topline results ("April 2020 Results Presentation");

g. July 22, 2020 call to discuss Biogen's Q2 2020 earnings ("Q2 2020 Call");

h. July 29, 2020 presentation of aducanumab Phase III topline results at the Alzheimer's Association International Conference ("July 2020 Results Presentation");

i. September 19, 2020 presentation of aducanumab Phase III topline results at the 23rd Chinese National Conference of Neurology ("September 2020 Results Presentation").

V. BACKGROUND

A. The Amyloid Hypothesis

52. In patients suffering from Alzheimer's disease, brain cells that process, store and retrieve information degenerate and die. Yet while Alzheimer's progression is reasonably well understood, its causes remain unclear.

53. First proposed in 1991, the amyloid hypothesis attributes the disease to build-up of a protein called amyloid beta.

54. Amyloid beta is a fragment of a larger protein, amyloid precursor protein, commonly known as APP. APP is produced in large quantities in neurons. When it functions normally, it is quickly cleaved into various proteins and metabolized.

55. One form of cleavage results in the production of single amyloid-beta molecules (monomers). Single amyloid beta molecules are easily metabolized because they are water soluble. But in some circumstances, the amyloid-beta producing cleavage is sufficiently regular to produce amyloid beta at high concentrations. The amyloid beta form into toxic amyloid groups, called oligomers. At very high concentrations, the amyloid beta can also form into larger insoluble chains, which eventually accumulate into amyloid plaques.

56. The amyloid hypothesis posits that either the oligomers or the plaque are responsible for Alzheimer's disease. Certain researchers believe that the amyloid plaque causes

surrounding neurons to develop intercellular tangles of a protein called tau. The tangles block the neurons' transport system, harming synaptic connections (the junctions between two nerve cells). More recently, most researchers have come to believe that the oligomers may cause Alzheimer's by diffusing into synapses and destroying them. Under either version of the theory, the deterioration of synaptic connections caused by amyloid beta oligomers or plaque causes loss of cognition and the other symptoms observed in Alzheimer patients.

57. In the decades after its formulation, the amyloid hypothesis displaced older theories, becoming the leading theory explaining Alzheimer's. Billions of dollars were spent researching potential cures based on the amyloid hypothesis. According to a 2017 review, more than a hundred products were tried or advanced to clinical trials.[5] These products targeted nearly every molecule the amyloid hypothesis suggests may assist in treating or preventing Alzheimer's disease, from molecules that inhibit the gamma secretase and BACE-1 molecules that drive production of amyloid beta, through monoclonal antibodies that inhibit the formation of amyloid plaque or break it up, to drugs that inhibit other molecules with which amyloid beta interacts. Yet none succeeded.

58. These failures have taken a toll on the amyloid hypothesis itself. A growing minority of researchers and practitioners dispute the theory.

B. How Aducanumab Works

59. Aducanumab is a monoclonal antibody, which is a laboratory-made clone of naturally-occurring antibodies.

[5] Dev Mehta et al, *Why do trials for Alzheimer's disease drugs keep failing? A discontinued drug perspective for 2010-2015*, available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5576861/

60. Antibodies are proteins that circulate through the body until they find, and attach to, other proteins known as antigens. The antibody thereby draws the immune system cells' attention to the protein, which these cells then destroy.

61. According to Defendants, what the decades of failed amyloid-based treatments showed was that the human body could not safely tolerate the high doses of antibodies necessary if the antibodies targeted *all* forms of amyloid beta. Defendants claimed that Biogen had learned the lesson of these failures. Aducanumab does not target all amyloid beta. Instead, it selectively targets *aggregated* amyloid beta, with little or no unproductive binding to amyloid beta monomers. By more precisely targeting aggregated amyloid beta, Defendants claimed, aducanumab can be given in doses high enough to be clinically effective.

62. Amyloid beta aggregates in two principal different forms, soluble oligomers or the insoluble fibrils which make up plaque. Of these, aducanumab preferentially targets fibrils.

C. Aducanumab's Death and Revival

63. ***"It's make-or-break for the company. I can't think of more of a defining event for a large-cap company."***

-Brian Skorney, Robert W. Baird & Co. analyst, concerning the Aducanumab Advisory Committee Meeting

64. ***"So is there any product in any pipeline from any company that can be at par with aducanumab and can compensate for potential failure of such a major product? So I don't think so."***

-Defendant Vounatsos at the J.P. Morgan Healthcare Conference, shortly before futility was declared

65. ***"[Biogen] is basically a declining business. In the case of an aducanumab non-approval, it just becomes a very difficult investment story."***

Mohit Bansal, Citigroup analyst, as reported in February 5, 2021 *Reuters* article

i. Death

66. Biogen submitted an Investigational New Drug (IND) Application to the FDA for Aducanumab in 2011 and began Phase I trials shortly thereafter.[6]

67. Biogen's first study, Study 101, was a Phase I ascending dose study of 53 subjects. Single doses ranging from 0.3 to 60 mg/kg of aducanumab, or placebo, were administered to patients with mild to moderate Alzheimer's disease on a randomized and blinded basis.

68. Biogen used the safety data from Study 101 to inform Study 103 (also called PRIME), the Phase Ib/2 study that began in 2012 and yielded results beginning in 2014.

69. Study 103 included a 12-month randomized, double-blind, placebo-controlled period, followed by a dose-blinded long term exposure period. A total of 196 participants at 27 clinical locations across the United States were randomized and dosed.

70. The subjects were 50 to 90 years old and had early symptomatic Alzheimer's disease and PET-confirmed brain amyloid pathology.

71. A particular form (or allele) of a gene that codes for the production of apolipoprotein E (ApoE), a protein, is associated with higher rates of Alzheimer's. Each person inherits two forms of ApoE, one from each parent. Having one ApoE ε4 gene (APOE4) (25% of

[6] Because aducanumab is a biologic, Biogen must file a Biologics License Application (BLA) for its approval. But the clinical trials that lead to a BLA are the same as those that lead to a New Drug Application.

the population) increases the risk of Alzheimer's disease; having two (2-3%) increases the risk even further.

72. APOE4 is a risk factor, not a death sentence, because not every APOE4 carrier (Carrier or APOE4 Carrier) develops Alzheimer's disease, and not everyone who develops Alzheimer's disease is a Carrier. Still, APOE4 is a potent risk factor. Even though only about one quarter of the population are Carriers, almost half of all Alzheimer's disease patients are.

73. Carriers are also at increased risk of amyloid-related amyloid imaging abnormalities (ARIA), including the very serious ARIA-E. Because ARIA is a known side effect of anti-amyloid beta monoclonal antibodies like aducanumab, Carriers risk getting ARIA, particularly with higher aducanumab doses.

74. Study 103 included both Carriers and Non-Carriers. One cohort, which consisted solely of Carriers, was designed to assess whether the incidence of ARIA could be mitigated through titration.[7]

75. Study 103's primary endpoint was the safety and tolerability of aducanumab. Secondary endpoints were (1) the effect of aducanumab on brain amyloid content; (2) the pharmacokinetics of aducanumab; and (3) the immunogenicity of aducanumab. Exploratory endpoints included measures of clinical efficacy, such as change from baseline on the Clinical Dementia Rating – Sum of Boxes (CDR-SB) and Mini-Mental State Examination (MMSE) tests. Biogen later used both CDR-SB and MMSE as endpoints in aducanumab's Phase III trials.

[7] Drug titration is the process of adjusting the dose of a medication for the maximum benefit without adverse effects. It is especially important when the range between the dose at which a drug is effective and the dose at which side effects occur is small.

76. According to Biogen, four major findings from Study 103 influenced the design of the two Phase III trials that would begin in 2015: (1) Biogen identified 10 mg/kg as the most effective dose of aducanumab; (2) Biogen found the CDR-SB scale to be sensitive enough to detect changes among early symptomatic Alzheimer's patients; (3) Biogen observed greater variability on the CDR-SB among patients with more advanced disease at baseline; and (4) in 2016, Biogen concluded that titration did lower the incidence of ARIA in Carriers as compared to fixed dosing.

77. Study 301 (i.e., ENGAGE) and Study 302 (EMERGE) were identical global randomized double-blind, placebo-controlled parallel Phase III studies designed to show aducanumab's safety and efficacy. These two Phase III trials included an 18-month double-blind placebo-controlled period, followed by a dose-blinded long term extension period.

78. Together, Studies 301 and 302 enrolled 3,285 patients at 348 sites across 20 countries. Participants were between 50 and 85 years old, with early symptomatic Alzheimer's disease, and positive for brain amyloid pathology as assessed by positron emission tomography (PET). Approximately 80% of participants in each Study would have a baseline clinical diagnosis of mild cognitive impairment, and approximately 20% would have a diagnosis of mild Alzheimer's disease dementia, the latter of which denotes patients whose Alzheimer's disease substantially interfered with daily life.

79. Both Carriers and Non-Carriers were enrolled, with Carriers by design accounting for approximately two-thirds of each study population.

80. Clinical measures were evaluated at baseline, 6 months, 1 year, and 18 months.

81. While Studies 301 and 302 were identical in design, they started one month apart, with Study 301 beginning first and remaining ahead in enrollment.

(1) Clinical endpoints

82. Once symptoms become noticeable, patients with Alzheimer's disease experience progressive decline in cognition and brain function. Biogen selected five clinical efficacy scales to measure the range of symptoms experienced by patients with Alzheimer's disease. Assessments on these five scales relies on information provided by the patient, the caregiver, and independent clinical assessors. On each of these five scales, the total measures disease severity, with changes over time reflecting the clinical progression.

(a) CDR-SB

83. The studies' primary endpoint was the change from baseline in CDR-SB at Week 78. The CDR-SB scale integrates assessments from three domains of cognition (memory, orientation, and judgment/problem-solving) and three domains of function (community affairs, home/hobbies, and personal care).

84. After interviewing the caregiver and examining the patient, the rater assigns a score that best describes the patient's current level in each of these six domains. The "sum of boxes" scoring methodology adds up the scores for each of the six domains, and provides a value ranging from 0 to 18 that can change in increments of 0.5. Higher scores indicate greater severity of Alzheimer's disease.

(b) MMSE

85. The first-ranked secondary efficacy endpoint was the change from baseline in MMSE at Week 78. MMSE is a performance-based test of global cognitive status. The test consists of 11 tasks to assess orientation, word recall, attention and calculation, language abilities, and geospatial functions. The 11 tasks produce scores that are combined to obtain a total score, which ranges from 0 to 30. Lower scores indicate higher cognitive impairment.

(c) ADAS-Cog13

86. The second-ranked secondary efficacy endpoint was the change from baseline in ADS-Cog13[8] at Week 78. ADAS-Cog13 includes both cognitive tasks and clinical ratings of cognitive performance. The test focuses on, among other things, word recall, ability to follow directions, ability to copy or draw an image, ability to interact with everyday objects, naming, word recognition, memory and concentration. The total scores range from 0 to 85, with a higher score indicating higher cognitive impairment.

(d) ADCS-ADL-MCI

87. The third-ranked secondary efficacy endpoint was the change from baseline in ADCS-ADL-MCI[9] at Week 78. In the ADCS-ADL-MCI test, caregivers rate patients' actual functioning over the previous month on a series of 18 items (ranging from shopping, preparing meals to getting dressed), and assess changes in the functional state of the patients over time. The score ranges from 0 to 53, with lower scores reflecting functional deterioration.

(e) NPI-10

88. The studies' tertiary efficacy endpoint was the change from baseline on NPI-10[10] at Week 78. In NPI-10, an interviewer compiles an index of the presence, frequency and severity of 10 neuropsychiatric symptoms, including delusions, hallucinations, depression, anxiety and euphoria. The score ranges from 0 to 120, with higher scores indicating more serious symptoms.

(2) Biomarkers

[8] Which stands for Alzheimer's Disease Assessment Scale - Cognitive 13-Item Scale.

[9] Which stands for Alzheimer's disease co-operative study ADL scale for mild cognitive impairment.

[10] Which stands for 10-item Neuropsychiatric index.

89. In addition to the clinical measures, various biomarkers were assessed to study the effects of aducanumab on brain pathology. PET scans were conducted on a subset of patients to determine whether patients receiving aducanumab showed greater reduction in amyloid plaque in their brains than patients receiving placebo. In turn, Biogen could determine whether removal of amyloid plaque correlated with better clinical outcomes – i.e., whether aducanumab worked as intended.

(3) Doses Studied

90. The Phase III studies compared the effects of two dosing regimens of aducanumab versus placebo over the 18-month placebo-controlled period. Participants were randomized 1:1:1 to aducanumab high dose, aducanumab low dose, or placebo. The randomization was stratified by APOE4 status.

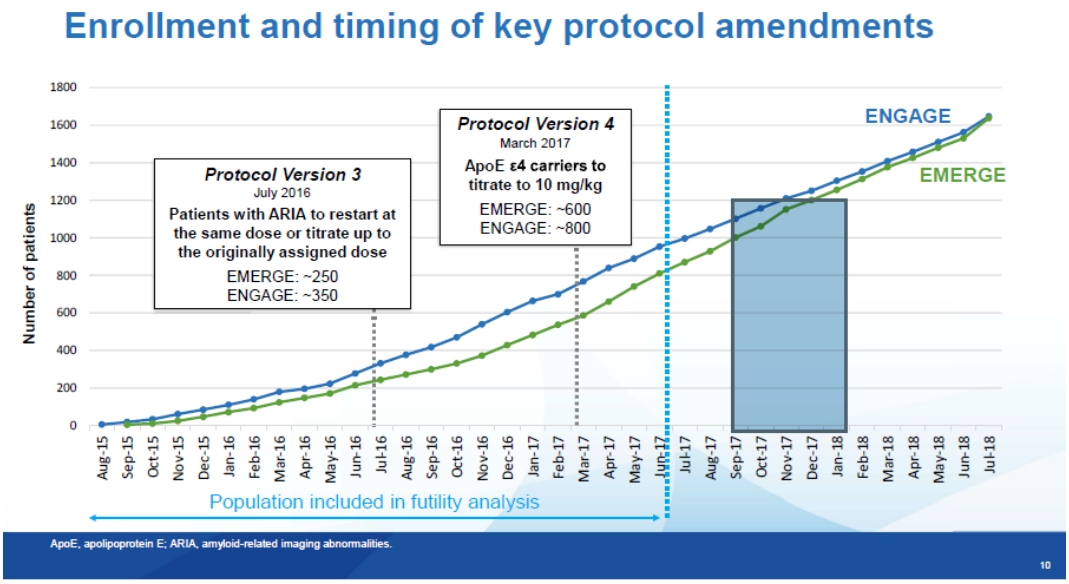
91. Initially, due to concerns about Carriers' risks of developing ARIA, both the low and high doses of aducanumab differed based on the participant's APOE4 status.

92. At the beginning of the studies, Carriers assigned to the low dose received 3 mg/kg after titration over 8 weeks, while Non-Carriers assigned to the low dose received 6 mg/kg after titration over 24 weeks.

93. Similarly, at the beginning of the studies, Carriers assigned to the high dose received 6 mg/kg after titration over 24 weeks, while Non-Carriers assigned to the high dose group received 10 mg/kg after titration over 24 weeks.

(4) Amendments

94. Biogen implemented two important amendments to the protocol during the course of the studies, both due to diminishing concern surrounding ARIA as a side-effect of aducanumab.



(5) Timing of Protocol Version 3 and Protocol Version 4

(a) Protocol Version 3

95. The first amendment, documented in Protocol Version 3 (PV3), took place in July of 2016 and related to ARIA management.

96. The Phase III trials began with an ARIA management program that resembled the one that had been used in Study 103. This protocol mandated suspending dosing under certain circumstances, for example when ARIA was accompanied by mild or moderate symptoms, or when ARIA-E was radiographically moderate or severe. After ARIA was resolved (i.e., disappeared), dosing could be resumed at the next lower dose. These participants were required to remain at that dose for the duration of the trial. For other participants, for example those with more severe symptoms, dosing was discontinued permanently.

97. PV3 made several changes to the protocol. Under PV3, participants who had suspended dosing due to ARIA that was later resolved could resume dosing at the same dose (rather than the lower dose) and could continue titration to the target dose. In addition, participants with certain severe symptoms could suspend dosing (rather than discontinuing permanently).

98. PV3 therefore enabled participants who had experienced ARIA, who were almost entirely APOE4 Carriers, to continue on aducanumab and reach their assigned target dose of aducanumab.

(b) Protocol Version 4

99. Protocol Version 4 (PV4) was adopted in March 2017 based on ARIA data from the final enrolled cohort of Study 103 which showed that 10mg/kg doses could be safely administered to APOE4 Carriers. With this data in hand, PV4 increased the high dose for Carriers from 6 mg/kg to 10 mg/kg. The low dose did not change.

100. Thus, after PV4, the high dose of aducanumab, after titration over 24 weeks, was 10 mg/kg for all participants regardless of APOE4 status.

(6) Futility Analysis

101. An interim analysis for futility was included in the Phase III study protocol to terminate the studies early if the analysis showed that aducanumab was unlikely to prove effective.

102. The protocol specified that the interim futility analysis would be performed after approximately 50% of participants in the studies had the opportunity to complete the Week 78 primary efficacy assessment. The data cutoff date for the prespecified futility analysis was December 26, 2018.

103. An independent group, external to Biogen and not involved in the conduct of the studies, performed the futility analysis.

104. The prespecified criteria for futility was based on conditional power for CDR-SB, which is the probability calculated on the data at the interim date that the final data would show statistical significance in favor of aducanumab.

105. The studies would be considered futile if the trials had less than a 20% chance of meeting primary endpoints, pooling the data across both trials (called conditional power). This meant that if there were less than a 20% likelihood that final study results would be statistically significant in both the low and high dose arms of Studies 301 and 302, the studies would be terminated. The conditional power for each study was calculated on a future estimate based on pooled data from Studies 301 and 302.

106. Biogen decided to use pooled data because of the statistical notion that pooling approach is better than examining the trials separately so long as the trials are relatively homogeneous. Because the two Phase III trials were identically designed, Biogen did not expect significant heterogeneity between the trials.

107. The futility analysis showed that the estimated conditional power values for CDR-SB in the high dose group were 12% for Study 302, and 0% for Study 301. The probability of a statistically significant difference at the end of the Study was therefore well below the prespecified cutoff of 20%.

108. Because the futility criteria had been met, Biogen terminated aducanumab's Phase III trials. In a press release issued on March 21, 2019 announcing the termination, Biogen explained that "[t]he decision to stop the trials is based on results of a futility analysis conducted by an independent data monitoring committee, which indicated the trials were unlikely to meet their primary endpoint upon completion."

109. On this news, the price of Biogen stock fell from its previous close of $320.59 to $226.88, or by over 29%, on March 21, 2019.

110. The analysts who covered Biogen immediately slashed their price targets in response:

Analyst	Price target reduction	Source
SVB Leerink	From $341 to $247	March 22, 2019 report titled *Post-Aducanumab Future Uncertain; Changes Needed But How & When?*
RBC Capital Markets	From $318 to $236	March 22, 2019 report titled *[Biogen] Without Alzheimer's: What's Next and Where Do They Go From Here?*
Morgan Stanley	From $401 to $210	March 22, 2019 report titled *Base Business Risks No Longer Offset By Significant Upside Optionality*
BMO Capital Markets	From $322 to $250	March 22, 2019 report titled *Little Right Now to Cling to*
Wells Fargo Securities	From $455 to $270	March 21, 2019 report titled *Downgrading to Market Perform on Alzheimer's Failure*
UBS	From $395 to $242	March 21, 2019 report titled *The Day After – Where to From Here?*
Oppenheimer	From $375 to $290	March 21, 2019 report titled *Post-Aducanumab, Attention Shifts to Cash Flows*
J.P. Morgan	From $436 to $244	March 21, 2019 report titled *Much Adu About Everything: Failed Phase 3 Futility Analysis Delivers Big Blow to [Biogen]*
Cantor Fitzgerald	From $400 to $250	March 21, 2019 report titled *Increased Risk after [Alzheimer's Disease] Failure*
Canaccord Genuity	From $396 to $275	March 21, 2019 report titled *Aducanumab failure means [Biogen] at a strategic crossroads*
Barclays	From $340 to $250	March 21, 2019 report titled *More Optionality Needed*

111. Investors made clear to Biogen that it had to come up with a game-changing new drug or they would head for the exits. As a Jefferies analyst wrote in an April 24, 2019 report:

> Key Takeaway
> Management addressed three issues on the Q1 call: Tec IPR, Spinraza competition, and BD/M&A. Yet the most common investor question we receive relates to the potential for a near-term catalyst to get excited about. Investors who thought there might be near-term "value creation" or "strategic alternatives" were left with nothing to cling to as comments focused on continued [stock] buybacks and long-term pipeline diversification.

112. Many analysts feared aducanumab's failure left Biogen dead. J.P. Morgan made Biogen the first profile in its *The Excavator* series of reports on companies that seemed to be heading to extinction. J.P. Morgan's report spanned more than 100 pages and began:

> So what does the future hold [for Biogen]? First and foremost (and maybe most obvious), the outlook for top-line growth appears challenged, with MS, SMA, and royalty revenue all at risk and a lack of exciting, de-risked pipeline candidates ready to step up. Secondly, it's clear from our conversations that investors are waiting for Biogen to bring in some late-stage assets with tangible value; however, for a number of reasons (willingness, cost / availability of targets, etc.), this could be an uphill battle and may never even materialize (sometimes you just have to trust what you see). Further complicating matters – at least for the short term – is the lingering uncertainty around Tecfidera IP. With all of this on the horizon, we struggle to get constructive on the name and believe that the onus is on management to change this dynamic.

113. J.P. Morgan's *The Excavator* report on Biogen was published on October 9, 2019. Three weeks later, Defendants announced aducanumab's revival.

114. During the Class Period, investors were laser-focused on aducanumab. In a note sent to clients on or about April 21, 2020, an analyst employed by Jefferies wrote that "[f]or every question related to fundamentals, we get 10 questions on Alzheimer's status."

115. In a report dated July 8, 2020, a J.P. Morgan analyst wrote that "with mounting pressures on the core MS/SMA franchises lowering [Biogen]'s perceived floor valuation, everything appears to be riding on this single, controversial asset [aducanumab]."

116. And in a November 3, 2020 article, a Wolfe Research analyst wrote: "By our modeling at least, [Biogen] lives and dies by how aducanumab plays out. This is because [Biogen]'s underlying revenue base is like quicksand due to patent expiries and competitive threats."

ii. Sandrock and Head of the FDA's Office of Neurology Billy Dunn Meet Secretly Off-the-Books to Discuss Aducanumab Approval

117. Biogen inappropriately manipulated an FDA Office desperately seeking to approve a treatment for Alzheimer's disease.

118. Biogen continued to collect data between the December 28, 2018 futility cut-off and its futility declaration on March 21, 2019. According to an October 22, 2019 Bloomberg article titled *How Biogen Salvaged Its Alzheimer's Drug After a Costly Failure*, after declaring futility, Biogen tasked 49 of its statisticians to pore over the Phase III results and salvage any data that could support aducanumab's approval.

119. According to a June 23, 2021 STAT News article,[11] in or around May 2019, Defendant Sandrock covertly approached the head of the FDA's Office of Neurology, Billy Dunn, about aducanumab.

120. Both Sandrock and Dunn were attending the American Academy of Neurology 2019 Annual Meeting held in Philadelphia from May 4-11, 2019.

121. Sandrock and Dunn used the occasion to meet secretly. Their meeting was off-the-books and off-the-record, in violation of FDA practice. Its existence was not publicly known until the STAT article.[12]

122. At the meeting, Sandrock told Dunn he believed aducanumab might slow Alzheimer's progression. Sandrock asked Dunn whether he would consider helping find a way to approve aducanumab.

[11] STAT news is a biotech specialist publication sponsored by Boston Globe Media, the same company that publishes the Boston Globe. The STAT article is attached hereto as Exhibit 1.

[12] In a July 20, 2021 article, the *New York Times* confirmed STAT's reporting of the off-the-books, off-the-record meeting. The *New York Times* article is attached hereto as Exhibit 2.

123. Dunn must have agreed, because shortly after the meeting, Biogen created Project Onyx, an effort to obtain FDA approval of aducanumab despite Biogen's and the trials' independent data monitoring committee's analyses showing the trials were futile.

124. Dunn's immediate agreement reversed the FDA's previous plan to evaluate aducanumab. As the minutes of the December 2014 Meeting between the FDA and Biogen show, the FDA had told Biogen it would not approve aducanumab if Studies 301 and 302 showed discordant results:

> The Agency had no objection in principle to [conducting two parallel Phase III studies]; however, the Agency also observed that should only one of the two studies then be positive, and the other study negative, for efficacy (and assuming the primary efficacy measures used in those studies are appropriate), ***such results would not ordinarily support the approval of [aducanumab] for an indication similar to that which the sponsor is currently pursuing.***

125. Though the off-the-books meeting reversed the FDA's on-the-books determination so as to make aducanumab's approval possible, Biogen and the FDA's public account of their collaboration on aducanumab approval omits it entirely. Rather, Biogen and the FDA told the Advisory Committee in public materials that the collaboration began later when Biogen provided data to the FDA:

> **3.3.2. Biogen-FDA Collaborative Investigation**
>
> Biogen shared the March 2019 results with the FDA, seeking the Agency's counsel and expert opinion on the appropriateness and interpretation of the analyses.

iii. "It Was Clear That Billy Dunn Was An Ally, So the Job For Biogen Became Figuring Out How to Support His Efforts Within the FDA"

126. From then on, Biogen focused on providing ammunition to Dunn to support his efforts to make the FDA approve aducanumab regardless of the clinical data. As one former Biogen employee told STAT, "[i]t was clear that Billy Dunn was an ally, so the job for Biogen became figuring out how to support his efforts within the FDA." Another former employee with

knowledge of Biogen's interaction with Dunn and other FDA officials told STAT that "I knew from the interest levels within FDA that the agency was always going to find a way to approve Aduhelm."

127. By mid-May, Biogen was sharing clinical data and other information with FDA officials.

128. The stage was set for the June 14, 2019 (on-the-books) Meeting between Biogen and the FDA, led by Dunn. According to the STAT article, at the meeting, before seeing any additional analyses, Dunn's office gave Biogen the roadmap it sought. The FDA presented Biogen five different pathways to approval. The FDA did not consider the possibility that aducanumab might not be approved.

129. The meeting minutes, which were later published, confirm the STAT article. At the meeting, the FDA presented five "options" Biogen could pursue after conducting further analyses:

> A number of potential options may be available, depending on the results of additional analyses already available. These additional analyses would largely be the focus of the collaborative working group. The following 5 options were discussed[.]

130. One of the options was that "[a]dequate evidence exists to conclude that aducanumab is ineffective", though usually the applicant bore the burden of proving efficacy. Moreover, the summary of the discussion made clear that the FDA had already ruled out that "option":

> The termination of the clinical development of aducanumab as a treatment for Alzheimer's disease would be predicated on a conclusion that adequate evidence exists to establish that

> aducanumab is ineffective (or is highly likely to be ineffective) for the treatment of Alzheimer's disease. ***For the reasons noted above, that is not the case.***[13]

131. Thus, by June 14, 2019, Dr. Dunn had already decided to approve aducanumab. He would spend the following two years pushing it through approval no matter what the data showed.

132. The FDA and Biogen's joint presentation to the Advisory Committee falsely claims the FDA had not made up its mind by the June 2019 Meeting. It provides:

> At this meeting, the FDA concluded in the minutes that "it would have been more appropriate if futility had not been declared for those studies." After noting that "the effect of early termination of the studies on the interpretability of the observed efficacy data and associated analyses ***is a matter for further detailed consideration***," the FDA further noted, "on face, that the effects of aducanumab in [Study 302] ***might*** not only be interpreted as being supportive of the efficacy of that compound in Alzheimer's disease, but ***might*** also be considered exceptionally persuasive on several of the instruments used to evaluate efficacy."
>
> The FDA noted, "Further complicating the interpretation of the available data for Studies 301 and 302 are the partially conflicting results … for Study 301 as compared with those for Study 302, with particular attention to the discordant high dose results of each study (while noting an apparent degree of consistency of the low-dose results between the studies). A detailed understanding, informed by plans for further analyses ..., of the overall results, and especially these discordant results, is critical to any ***consideration of whether*** Study 302 (with or without possible support from Study 301, as might be determined from further explorations of the data) ***might*** provide evidence adequate to establish the effectiveness of aducanumab for the treatment of Alzheimer's disease." The FDA further stated that "the submission of a marketing application for aducanumab based primarily on the results of Study 302 as a single positive efficacy study ***may also*** be considered. ***It is possible*** that the results of Study 301 ***may*** have a role in supporting the results of Study 302 or ***may*** be understood well enough to be dismissible (i.e., to not represent evidence that the drug is ineffective), ***assuming that further analyses do not lead to a conclusion that Study 301 is clearly negative.***"
>
> After citing the ***possibility*** that aducanumab ***could be*** an effective drug for the treatment of Alzheimer's disease based on the Study 302 data presented, the FDA stated, "It is imperative that extensive resources be brought to bear on ***achieving a maximum***

[13] The STAT article, published before the minutes, accurately reported that "Importantly to Biogen, a possible conclusion that Aduhelm was ineffective, based on the data at hand, was categorically ruled out by the FDA."

> ***understanding of the existing data***. Given the wholly unique situation that is the current state of the aducanumab development program …, those further analyses would best be conducted as part of a bilateral effort involving the Agency and sponsor, i.e., through a 'workstream' or a 'working group' collaboration."

133. Biogen and the FDA's disclosures to the Advisory Committee also greatly understated the scope of the collaboration between Biogen and the FDA. As set out in the STAT article, the FDA/Biogen collaborative group met or communicated almost daily in June, July, and August of 2019. The two worked to collect and analyze data for inclusion in aducanumab's BLA. The FDA and Biogen even jointly decided on which method they would use to push for aducanumab's approval. They decided to pursue standard FDA approval.

iv. Biogen Manipulates Study 301 Data

134. A company conducting clinical trials must specify a statistical analysis plan before the trials begin and the final determination of efficacy must be made based on the pre-specified clinical endpoints as analyzed in the pre-specified statistical analysis plan.

135. Hunting through the trial data and running statistical analyzes after the fact is usually considered unreliable and a form of data manipulation. Data from clinical trials can be analyzed in multiple ways. The practice known as "p-hacking" occurs where researchers try multiple analyses to yield a statistically significant result.

136. The "p" in p-hacking refers to the "p-value," a statistical measure that shows the probability of the study results by chance alone if no drug effect was present. The American Statistical Association defines a p-value as "the probability under a specified statistical model that a statistical summary of the data (*e.g.*, the sample mean difference between two compared groups)

would be equal to or more extreme than its observed value."[14] For example, in the context of clinical drug trials, tests of a drug intended to treat a certain disease may show that the incidence of the disease decreased among people who took the drug at a certain rate. The p-value represents the probability of seeing at least as much decreased incidence of disease as the trial showed, if the study drug had no effect. A p-value of 0.05 – by convention, the standard for deeming an effect "statistically significant" – means such a result would happen only 5% of the time.

137. What the p-value does ***not*** demonstrate is whether the drug actually had the intended effect, or to what extent it was effective. Rather, the p-value attempts to measure only how surprising the results would be if the drug were not effective.

138. By running multiple post-hoc analyses, a researcher can all but guarantee a statistically significant result. Just as someone rolling a twenty-sided dice will eventually roll a 20, researchers who run different post-hoc analyses on the population will eventually find one that shows the drug "worked". This is p-hacking.

139. To close the door to such manipulation, whether intentional or merely reflecting wishful thinking, in the United States, clinical trial endpoints must be specified and posted on www.clinicaltrials.gov before the trial begins.

VI. DEFENDANTS' CLASS PERIOD MISCONDUCT

140. On October 22, 2019, Defendants held a call to discuss Biogen's Q3 2019 earnings and aducanumab's apparent rebirth (i.e., the Q3 2019 Call). Then, on December 5, 2019, Defendants (a) presented aducanumab Phase III clinical trial results at the Clinical Trials on

[14] Ronald L. Wasserstein, *ASA Statement on Statistical Significance and P-Values*, The American Statistician, Volume 70, Issue 2, at 129-133 (2016), *available at* https://amstat.tandfonline.com/doi/full/10.1080/00031305.2016.1154108#.YHc4B-hKg2w ("*ASA Statement*").

Alzheimer's Disease conference (i.e., the December 2019 Results Presentation); and separately (b) held a call to answer investors' questions about aducanumab (i.e., the December 2019 Q&A). Defendants supported their claims with 58 slides of carefully selected data and specific statements.

141. In the Q3 2019 Call and December 2019 Results Presentation, Defendants presented selected data and made statements of fact designed to give the false impression that aducanumab clinical trials' outcome was favorable. Among other things, Defendants told an elaborate story that differences between patient populations of Study 301 and Study 302 showed that Study 301's results were not only dismissible, they supported approval.

142. Defendants omitted at least eight critical pieces of data and analyses from their public presentations that showed their statements were false or misleading:

Statements shown to be false by, or rendered misleading for failure to disclose, concealed data	**Data concealed**	**Fact shown by omitted data**
Patients achieved dose-dependent improvements in clinical outcomes	Clinical outcomes by APOE4 status	Non-Carriers patients achieved results statistically indistinguishable from placebo even though they consistently received 10mg/kg
Patients in Study 301 who were like Study 302 patients saw clinical benefits	Study 302 clinical outcomes by PV4 status	No difference in Study 302 clinical outcomes between Carriers who receive treatment before rather than after PV4
Patients achieved dose-dependent improvements in clinical outcomes and, in particular, patients benefited from uninterrupted treatment	Clinical outcomes by whether treatment was interrupted by ARIA event	Patients whose treatment was interrupted by ARIA achieved better clinical outcomes

Patients achieved dose-dependent improvements in clinical outcomes and, in particular, the total aducanumab received or the total number of 10mg/kg doses was associated with better clinical outcomes	Clinical outcomes by number of doses received	The number of 10mg/kg doses received had no impact on clinical outcomes in Study 302
There was a correlation between amyloid reduction and clinical outcomes; the amyloid reduction caused or "led to" improvements in clinical outcomes	Correlation between amyloid reduction and clinical outcomes	There was no correlation between amyloid reduction and clinical outcomes
Geographical factors had no meaningful impact on results	Breakdown of clinical outcomes by country	There were substantial variations in results by country and the U.S. did not see substantial, let alone statistically significant, improvements in clinical outcomes under any scenario
Aducanumab is effective early in the progression of Alzheimer's disease	Breakdown of clinical outcomes by age and disease severity	Younger patients and patients with less advanced Alzheimer's disease achieved worse outcomes
Secondary endpoints support approval	Correlation between secondary endpoints	Secondary endpoints were closely correlated to each other and the primary endpoint

143. By making false and misleading statements and concealing the data that would show the statements' falsity, Defendants defrauded investors.

A. Defendants Made False Statements Dose Response and Study 301

i. Defendants Could Not Secure Aducanumab's Approval Without Disarming the Negative Study 301 Results

144. Of the aducanumab clinical trials, one (Study 302) was potentially positive, while the other (Study 301) was clearly negative.

145. At the June 2019 Meeting, Biogen and Dunn's office discussed how they would secure approval of aducanumab. Biogen and Dunn's office decided that Biogen would seek, and the Dunn's office push for, regular approval.

146. The June 2019 Meeting's minutes set out two options under which the FDA could grant regular approval to aducanumab. Both options required that Biogen at least explain away the results of Study 301:

> [Collective discussion of Options] 2 and 3 – The submission of a marketing application for aducanumab based primarily on the results of Study 302 as a single positive efficacy study may also be considered. It is possible that the results of Study 301 may have a role in supporting the results of Study 302 or may be understood well enough to be dismissible (i.e., to not represent evidence that the drug is ineffective), assuming that further analyses do not lead to a conclusion that Study 301 is clearly negative. However, currently available data do not suggest the future use of Study 301 as an efficacy study providing independent evidence of effectiveness supporting the approval of aducanumab for the treatment of Alzheimer's disease. ***For both options 2 and 3, the results of further detailed analyses [of Study 301] would be expected to be critical supportive components that establish or contribute to the interpretability of the efficacy results.***

147. The market, likewise, understood that aducanumab's only pathway to approval was to explain away Study 301's results. There is no precedent for the FDA to approve a drug where one arm of Phase III trials was positive, and the other was negative, unless there is a reasonable explanation for the failure. As an October 29, 2019 report by an analyst employed by RBC noted:

> 3 key things need to happen for adu approval.
>
> * * * * *
>
> 2. FDA/EMA would need to buy into rationale for ENGAGE failure and be convinced EMERGE reflects adu's real activity.

ii. Defendants Made False Statements of Fact About 10mg/kg Dosing and Study 301 that Were Contradicted By Study 302 Data Defendants Concealed

148. To convince investors that aducanumab could receive regular approval, Defendants built a narrative, largely out of false and misleading statements, that patients in Study

301 who had received treatment similar to patients in Study 302 did experience improved clinical outcomes.[15] Defendants concealed the data showing their false and misleading statements, and their narrative, were false.

149. First, Defendants claimed that more patients in Study 302 were treated after PV4[16] than those in Study 301. Thus, more patients in Study 302 received a full complement of 10mg/kg doses rather than the reduced 6mg/kg pre-PV4 dose.

150. Then, Defendants claimed that the reason Study 302 ***was*** positive and Study 301 ***was not*** was that there were more post-PV4 patients in Study 302. Defendants claimed that Study 301's post-PV4 population achieved clinical outcomes similar to those achieved by patients in Study 302. Thus, Defendants claimed, aducanumab was effective when patients received 10mg/kg; it was not effective when patients received a lower dose. Then, Defendants claimed patients experienced a dose-dependent response to aducanumab that depended on receiving uninterrupted doses.

151. In truth, the data Defendants concealed showed that all the statements in the above paragraph were false. Unlike the public, the FDA was provided with individual patient data. The data was provided to the FDA's Office of Statistics. The Office of Statistics' Dr. Tristan Massie and his staff created a report breaking down and analyzing the data for specific critical subgroups, a draft of which was publicly filed in connection with the Advisory Committee meeting ("Draft Massie Report"). The Draft Massie Report revealed the data Defendants had concealed and

[15] Paragraphs 171 through 196 below set out the specific false or misleading statements that make up Defendants' narrative and the reasons they are false or misleading.

[16] Patients who consented to PV4 before week 16 of their treatment had the opportunity to be titrated to 14 doses of 10mg/kg. Thus, pre- and post-PV4 refers to those patients who adopted PV4 on or before their week 16.

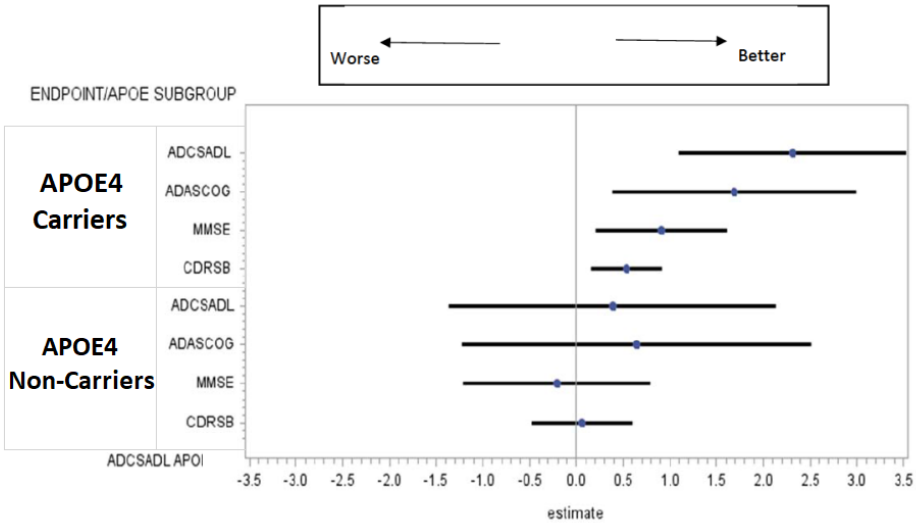
showed that key statements Defendants made to support their narrative were false or misleading. Indeed, the Draft Massie Report showed that substantially all the reasons Defendants say caused post-PV4 patients to achieve better outcomes in Study 301 had no impact in Study 302. It was not PV4, but the inevitable consequence of p-hacking, that explained Study 301's failure.

152. *First*, Defendants concealed the breakdown of patient responses by APOE4 status. The risk of ARIA was much greater among Carriers than Non-Carriers. So Carriers had always been titrated to 10mg/kg. They had always received what Defendants called the effective dose. Nor were their doses interrupted by ARIA events, because Non-Carriers were not susceptible to ARIA. So if Defendants' statements were true and not misleading, Non-Carriers should have achieved clinical outcomes better than Carriers both before PV4 (because Non-Carriers received full doses) and after (because Carriers' doses were not interrupted).

153. Yet the difference in clinical outcomes between high dose Non-Carriers and the placebo group was not only statistically insignificant, it was virtually nil. Though concealed by Defendants, on average, Non-Carriers' clinical outcomes were better than placebo by only 0.066 points on the 18-point CDR-SB scale. This was a negligible difference that did not even suggest an aducanumab effect, let alone show one with statistical significance:

Group	Study	Estimated CDR-SB point difference vs. placebo
Non-carriers	301	0.067
	302	0.065
	Pooled	***0.066***
Carriers	301	-0.07
	302	0.54
	Pooled	***0.23***

154. Indeed, in Study 302, Carriers achieved better clinical outcomes than Non-Carriers on all endpoints.



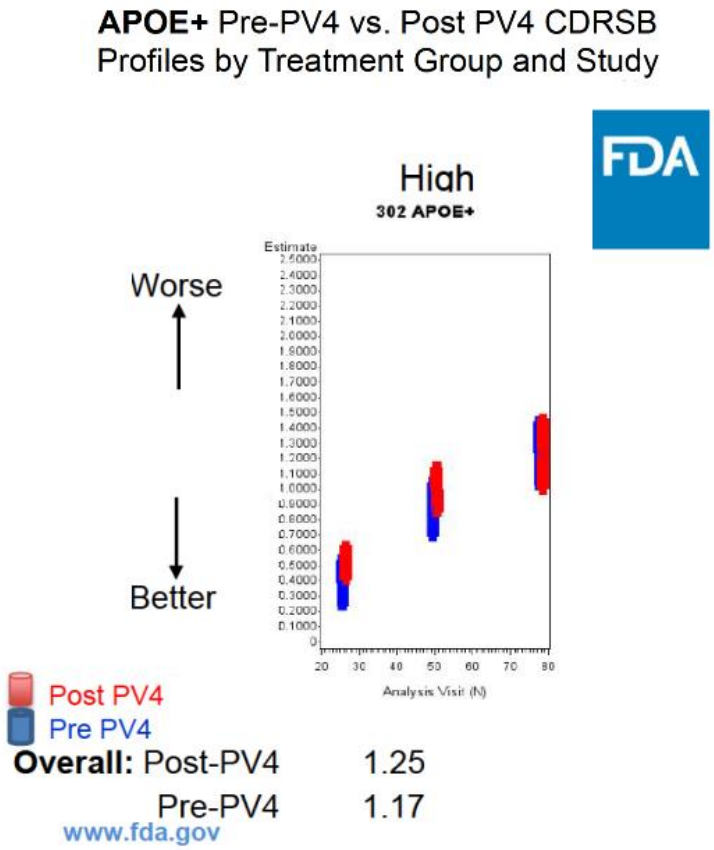
155. Further, that Non-Carriers did not see improvements in Studies 301 and 302 is inconsistent with Study 103. There, the difference in CDR-SB scores between placebo and high dose for Non-Carriers (1.63) was nearly twice as high as the same difference for Carriers (0.88). Thus, though Defendants claimed Study 103 supported Study 302' results, the trials are not even consistent.

156. Thus, the breakdown of clinical outcomes by APOE4 status shows that, among other things: (a) patients did not achieve a dose-dependent clinical improvement from aducanumab; and (b) 10mg/kg was not an effective dose.

157. *Second*, Defendants concealed the breakdown of Study 302 clinical outcomes by whether the patient was dosed before or after PV4. Defendants maintain that Study 302 was positive, and Study 301 negative, because more Carriers in Study 302 were dosed after PV4. If

Defendants' were statements true, then in Study 302, Carriers who were dosed after PV4 should achieve much better clinical outcomes those who were dosed before.

158. Yet in Study 302, Carriers did not experience better clinical outcomes after PV4:



159. In fact, in Study 302, Carriers experienced slightly higher increases (worsening) in CDR-SB scores after PV4. In Study 302, before PV4, the mean CDR-SB increase in APOE4 carriers was 1.17 points. After PV4, the mean increase rose to 1.25.

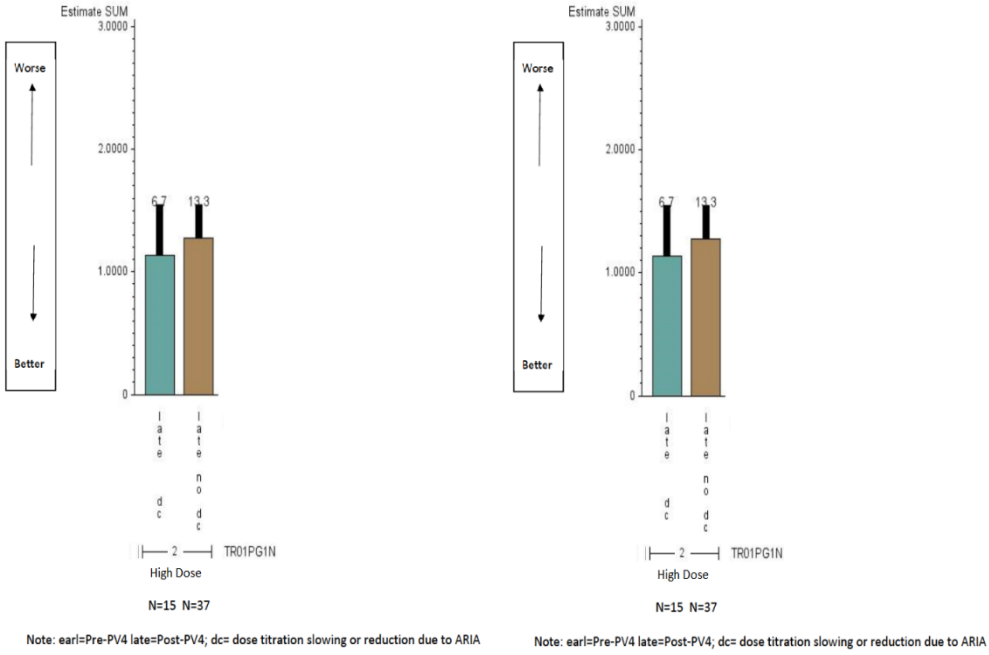
160. Further, in Study 302, Carriers achieved statistically significant improvements in clinical outcomes *before* PV4.

161. Thus, the breakdown of clinical outcomes by PV4 status in Study 302 shows that, among other things: (a) patients did not achieve a dose-dependent clinical improvement from

aducanumab; (b) Carriers who were dosed after PV4 did not achieve outcomes similar to Carriers in Study 302 because in Study 302 all Carriers achieved similar outcomes regardless of dose.

162. *Third*, Defendants concealed the breakdown of patient results based on whether their treatment was interrupted. As part of their claim that dosage that patients showed a dose-dependent reaction to aducanumab, Defendants maintained that interrupting treatment, most commonly because of ARIA, worsened patient outcomes. Because the cumulative dose is critical under Defendants' telling, these patients with dose interruptions should experience worse clinical outcomes on average than patients whose dose was not interrupted. Yet in both Studies 301 and 302, patients whose high-dose treatment was interrupted by ARIA and so received *fewer* high doses achieved numerically better outcomes than those whose treatment was not interrupted and received more high doses:[17]

[17] After unblinding, Biogen inexplicably altered certain historical patient records. One patient whose treatment was discontinued because of ARIA saw his or her CDR-SB score retroactively increased (worsened) from 1.0 to 3.5. Another whose dose was not interrupted saw his or her CDR-SB score retroactively decreased from -0.5 to -1.0. Four patients who had been classified as pre-PV4 were also reclassified as post-PV4. As a result of these suspicious changes made after Biogen knew the study and individual patient results, the data Biogen submitted showed that in Study 302, patients whose titration was interrupted by ARIA achieved slightly worse CDR-SB results.



Note: Earl= Pre-PV4; Late= Post-PV4; dc= dose titration slowing or reduction due to ARIA

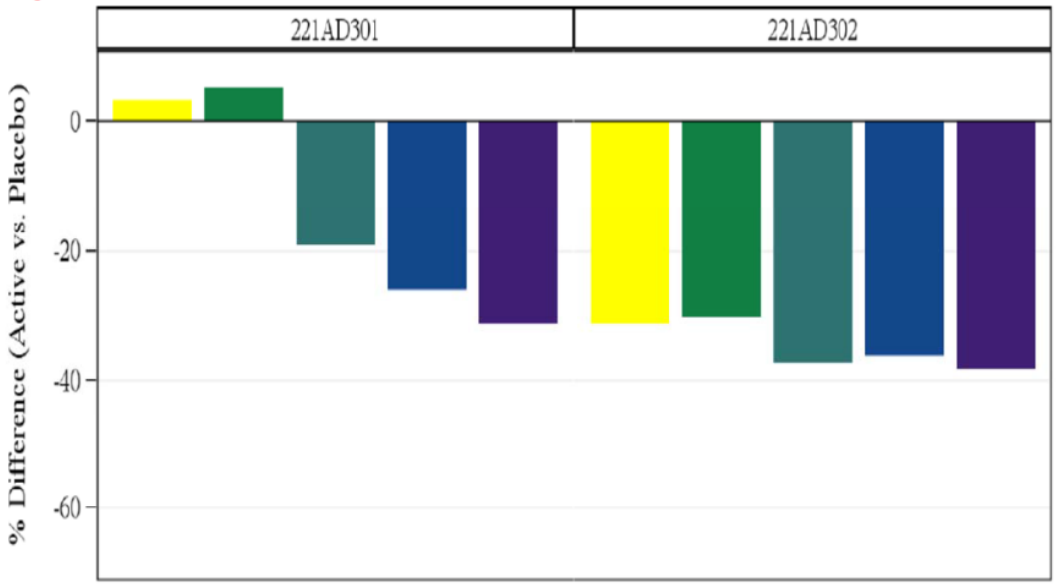
163. These facts show that *unblinding*, rather than aducanumab, accounted for the majority of the effect. Patients who experience ARIA will know it because they will be told as much by their doctors and their titration will be interrupted. ARIA is a side-effect of aducanumab, so these patients will also know that they are receiving aducanumab rather than a placebo, as will their caregivers. Knowing the patient received aducanumab rather than placebo may influence patient and caregivers' answers to interview questions, either by causing them to believe the patient performed better or by causing them to answer questions about how the patient functions in the world more favorably. Further, ARIA events may preselect patients willing to remain in the study because they are doing well. Because aducanumab's effect would be minimal even if aducanumab were effective, a significant unblinding effect would easily overwhelm any purported treatment effect.

164. Thus, the breakdown of clinical outcomes by whether treatment was interrupted by an ARIA event shows that, among other things: (a) patients did not achieve a dose-dependent clinical improvement from aducanumab; (b) a portion of the improvement of post-PV4 over pre-PV4 patients results from unblinding following ARIA events; (c) lack of interruption does not improve patient outcomes.

165. *Fourth*, Defendants concealed the breakdown of clinical outcomes by the number of doses received. As part of their claim that patients showed a dose-dependent reaction to aducanumab, Defendants maintained that patients needed to receive substantial numbers of 10mg/kg doses before they experienced a benefit from aducanumab.

166. Defendants' claim was false. In Study 302, the number of 10 mg/kg doses the patients received and the total dose did not matter at all:

Figure 13 Bar plot of CDR Sum of Boxes Adjusted Mean Change from Baseline Percent Difference from Placebo at Week 78 by Number of 10 mg/kg Doses, with Placebo Selected by Propensity Score Matching - ITT Population that have had Opportunity to Complete Week 78 by 20Mar2019: Placebo-controlled Period Excluding Data after 20Mar2019 – Nested Categories



Number of subjects and Adjusted mean at Week 78

Placebo	202	185	157	129	77	220	201	177	144	98
	1.42	1.36	1.49	1.54	1.58	1.56	1.45	1.54	1.38	1.41
BIIB037	202	185	157	129	77	220	201	177	144	98
	1.45	1.43	1.21	1.14	1.08	1.07	1.02	0.97	0.89	0.87

NOTE 1: Covariates in propensity score model include laboratory ApoE status, age, sex, baseline clinical stage, baseline scores of CDR-SB, MMSE, ADAS-Cog 13, ADCS-ADL-MCI, years of education, years since first AD symptom, AD symptomatic medication use at baseline, US/non-US and enrollment window of every 200 subjects. Placebo and treated subjects matched exactly on laboratory ApoE status. Subjects with undetermined laboratory ApoE status are grouped in the randomized ApoE subgroup.

NOTE 2: Results for each threshold were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

167. Thus, the breakdown of clinical outcomes by the number of doses received shows that: (a) patients did not achieve a dose-dependent clinical improvement from aducanumab; (b) more high doses do not improve patient outcomes.

168. As Dr. David Rind would later pointedly observe at a forum to discuss whether aducanumab is effective referenced in ¶333 below

> Biogen did to try to find why the negative trial got it wrong, and to make it look like the negative trial shows that high dose is better than low dose is better than placebo. But as

> soon as you do that, you cause the positive trial numbers to just look ridiculous. They don't make any sense at all. Why should we believe that analysis? Why should we believe that it's the negative trial that got it wrong and that, that explanation makes any sense?

iii. Defendants Succeeded in Misleading Investors About the Results of Study 301

169. When Defendants claimed that PV4 was responsible for the changes without disclosing the underlying data that would have shown their claim to be false, they actually misled investors, as shown by stock analyst reports:

a. In a December 6, 2019 report, a BMO analyst concluded that "[n]ew analyses of both EMERGE and ENGAGE demonstrated how the timing of [PV4] resulted in too few patients in the failed ENGAGE trial to ever achieve sufficient drug exposure. ***As shown on page 3, a[ducanu]mab treatment appears to result in the desired efficacy hurdle in the 'post-PV4' treated population of both studies***[.]"

b. In a December 5, 2019 report, a Cantor Fitzgerald analyst concluded that:

> ***When we look at ENGAGE data (the failed trial), we think that the argument of patients getting lower exposure to high dose does make sense.*** Biogen presented patient data post the protocol 4 amendment, and the outcomes were consistent between EMERGE and ENGAGE studies[.]"

c. In a December 5, 2019 report, a Morningstar analyst concluded that:

> One of the key questions going into the Dec. 5 presentation was whether the one-month difference in trial start dates for Engage and Emerge was big enough that the protocol amendment (allowing patients carrying that ApoE4 genetic risk to take the 10mg/kg high dose) could have prevented the more advanced Engage study from meeting its endpoints. Biogen disclosed that when this amendment was made in March 2017, Engage had 200 more patients enrolled than Emerge. As a result, fewer carrier patients received the high dose, resulting in 22% of patients receiving all possible 10mg/kg treatments in the Engage study, versus 29% in the Emerge study.
>
> ***Perhaps most importantly, Biogen provided a helpful analysis of only patients enrolled after the amendment, comparing patients in high-dose and low-dose arms of both studies to placebo patients. Among these high-dose patients, 51% in Emerge and 47% in Engage received all possible 10mg/ml [sic] doses, creating less difference in total dosing. This analysis revealed a 30% reduction in decline in CDR-SB in Emerge and a***

27% reduction in decline in CDR-SB in Engage for high-dose patients, which we think shows consistency between the trials and could be enough to support approval.

d. In a December 5, 2019 report, an RBC analyst concluded:

A few notably new datapoints which we believe were incrementally favorable. ***The most interesting new analysis, in our view, looked at patients post the Protocol 4 amendment [], in which the subgroup of [patients] eligible to potentially receive 14 doses of high-dose (10mg/kg) adu (and who consequently had 32% higher cumulative adu exposure) showed similar favorable CDR-SB benefits (27-30%) and benefits on other endpoints across the EMERGE and ENGAGE studies – helping build BIIB's case that ENGAGE's failure was actually due to the enrollment timing differences relative to the protocol amendments.***

e. In a December 5, 2019 report, a Guggenheim analyst concluded that:

[A]nalysis indicated that continuous exposure to high dose aducanumab provided consistent benefits to patients [in EMERGE] (this phenomenon was also present in ENGAGE (see figures below). In this vein, one [Key Opinion Leader] on the panel noted that based on the current dataset, he believed that more consistent exposure to higher doses over a sufficient duration of time could lead to more favorable patient responses.

f. In a February 3, 2020 report, an SVB Leerink analyst concluded:

Our View: We believe aducanumab could be the 1st [disease modifying therapy] approved for treating Alzheimer's, and it would be a significant product in AD.

* * * * *

- ***The high dose arms data are more impressive in the post-PV4 cohort when considering the enhanced treatment effect of [Placebo]-adjusted CDR-SB reductions (EMERGE moved from -23% in ITT to -30% for post-PV4, and ENGAGE moved from 2% in ITT to -27% for post-PV4)***

The SVB Leerink analyst concluded that higher doses after PV4 caused Carriers' clinical outcomes to improve:

- ***Initially, a suboptimal 6mg dose was applied in ApoE4 carriers due to ARIA safety concerns***
- ***After PV4, ApE4 [sic] carriers were titrated up to the 10mg dose to ensure enough exposure, as Biogen figured out that ARIA could be managed via careful dose titration; therefore, the data readouts were complicated by the modified clinical design***

170. Other analysts noted that the APOE4 Carrier/Non-Carrier subgroup analysis was material to aducanumab's prospects for approval and use:

a. In a December 5, 2019 report, a Cowen analyst noted that "[Biogen] did present a couple of new supportive efficacy analyses, but other subgroup analyses (e.g. APOE) were not disclosed".

b. In a December 5, 2019 report, a Credit Suisse analyst noted that "the lack of insight into how carriers (e.g. post-PV4) perform at high doses could prevent some physicians from prescribing without carrier testing[.]"

iv. Defendants' Specific False and Misleading Statements Seeking To Explain the Results of Study 301

171. On the October 22, 2019 call to discuss Biogen's Q3 2019 earnings and aducanumab's revival, Defendant Sandrock told investors:

> ***Our primary learning from these data is that sufficient exposure to high dose aducanumab reduced clinical decline across multiple clinical endpoints. This reduction in clinical decline was statistically significant in EMERGE, and we believe that patients – that the data from patients who achieved sufficient exposure to high dose aducanumab in ENGAGE support the findings of EMERGE.*** After consultation with the FDA, we believe that the totality of these data support a regulatory filing. ***Importantly, patients included in the futility analysis were those who had enrolled early in the trials and those early enrolling patients had a lower average exposure to aducanumab in large part due to two protocol amendments that occurred sometime after the start of the trials. These two protocol amendments were put in place precisely to enable more patients to reach high dose aducanumab, and for a longer duration. As a consequence, the larger dataset available after trial cessation included more patients with sufficient exposure to high dose aducanumab.***

172. Defendant Sandrock's emphasized statements were false because: (a) Non-Carriers exposed to 10mg/kg aducanumab doses did not achieve better clinical outcomes; (b) in Study 302, Carriers exposed to high doses did not experience better clinical outcomes after PV4 than before; (c) Carriers whose treatment including titration was interrupted did not experience worse clinical outcomes than Carriers whose treatment and titration were not interrupted; (d) Carriers who received more 10mg/kg aducanumab doses did not experience better clinical outcomes than Carriers who received fewer 10mg/kg doses; and, as a result, (e) "sufficient exposure" was only

correlated with improved clinical outcomes in one half (Carriers) of one arm (patients who received high doses) of one clinical trial (Study 301) of aducanumab's Phase III clinical trials; (f) the results from ENGAGE (Study 301) did not support EMERGE (Study 302) because the results of the two Studies were inconsistent in that the subset of post-PV4 Carriers carriers in Study 302 did not experience better results than pre-PV4 Carriers, thus preventing any conclusions from being drawn; and (g) Study 302 showed that Study 301 Carriers achieved better results after PV4 because of p-hacking, not aducanumab.

173. On the same call, Defendant Sandrock stated:

> ***So in other words, what I'm saying is that there is a very sort of sharp dose response, if you will, you have to get to high dose of aducanumab and intermediate dosing at least in an 18-month trial is not enough.***

174. Defendant Sandrock's emphasized statements were false because: (a) Non-Carriers exposed to 10mg/kg aducanumab doses did not achieve better clinical outcomes; (b) in Study 302, Carriers exposed to high doses did not experience better clinical outcomes after PV4 than before; (c) Carriers whose treatment including titration was interrupted did not experience worse clinical outcomes than Carriers whose treatment and titration were not interrupted; (d) Carriers who received more 10mg/kg aducanumab doses did not experience better clinical outcomes than Carriers who received fewer 10mg/kg doses; and, as a result; (e) there was no suggestion of a dose response except in one half (Carriers) of one arm (high doses) of one clinical trial (Study 301) of aducanumab's Phase III clinical trials; (f) in Study 302, Carriers who received full 10mg/kg doses did no better than those who received 6mg/kg doses at most, while Non-Carriers saw no clinical benefit at all; and (g) Study 302 showed that Study 301 Carriers achieved better results after PV4 because of p-hacking, not aducanumab.

175. Defendant Budd-Haeberlein stated on the Q3 2019 earnings call that "***dosing is a complex combination of duration, magnitude and no interruptions.***" Defendant Budd-Haeberlein added that "***you need to achieve high dose for long enough, but also have no interruptions, and so that's a more complex calculation between the two studies.***" Defendant Sandrock likewise stated on the call:

> I think that dose suspension in the context of an 18-month study was – it could be problematic, ***because they didn't achieve enough of the high dose***. But in clinical practice, we don't do 18-month treatment periods. We're going to treat patients for longer periods of time. And in that situation I think dose suspension may be acceptable in some patients.

176. Defendants Budd-Haeberlein and Sandrock's emphasized statements were false because: (a) Non-Carriers exposed to 10mg/kg aducanumab doses did not achieve better clinical outcomes; (b) in Study 302, Carriers exposed to high doses did not experience better clinical outcomes after PV4 than before; (c) Carriers whose treatment including titration was interrupted did not experience worse clinical outcomes than Carriers whose treatment and titration were not interrupted; (d) Carriers who received more 10mg/kg aducanumab doses did not experience better clinical outcomes than Carriers who received fewer 10mg/kg doses; and, as a result; (e) there was no suggestion that patients who achieved the "high dose" "for long enough" did better except in one half (Carriers) of one arm (patients who received high doses) of one clinical trial (Study 301) of aducanumab's Phase III clinical trials; (f) there was no suggestion that dose interruption had anything to do with clinical outcomes in any portion of any arm of any Phase III clinical study; (g) there was no suggestion of a dose response except in one half (Carriers) of one arm (high doses) of one clinical trial (Study 301) of aducanumab's Phase III clinical trials; and (h) Study 302 showed that Study 301 Carriers achieved better results after PV4 because of p-hacking, not aducanumab.

177. On the same call, Defendant Budd-Haeberlein stated:

> Aducanumab also demonstrated an impact on CSF biomarkers of tau pathology. A statistically significant reduction on CSF phospho-Tau levels was observed in EMERGE and ENGAGE with a dose proportional response in EMERGE. Aducanumab produced a numeric reduction in CSF total-Tau levels in EMERGE and ENGAGE with a dose proportional response in EMERGE. ***Although the primary and secondary endpoints were not met in ENGAGE in post analysis, the subset of patients who received sufficient exposure to 10 milligram per kilogram aducanumab in this case, at least 10 doses of 10 milligram per kilogram showed similar results to the comparable population from EMERGE, in terms of both amyloid plaque reduction and reduced clinical decline on CDR-SB.***

178. Defendant Budd-Haeberlein's emphasized statements were false because: (a) Non-Carriers exposed to 10mg/kg aducanumab doses did not achieve better clinical outcomes; (b) in Study 302, Carriers exposed to high doses did not experience better clinical outcomes after PV4 than before; (c) Carriers whose treatment including titration was interrupted did not experience worse clinical outcomes than Carriers whose treatment and titration were not interrupted; (d) Carriers who received more 10mg/kg aducanumab doses did not experience better clinical outcomes than Carriers who received fewer 10mg/kg doses; and, as a result (e) the results from ENGAGE (Study 301) were not similar to EMERGE (Study 302) because the results of the two Studies were inconsistent in Study 302, the subset of Carriers dosed after PV4 did not achieve better outcomes than Carriers dosed before PV4, thus preventing any conclusions from being drawn; and (f) Study 302 showed that Study 301 Carriers achieved better results after PV4 because of p-hacking, not aducanumab.

179. On the same call, Defendant Budd-Haeberlein stated:

> ***I think what we have learned clearly is that dose is very important, but that if individuals do receive 10 milligrams per kilogram then they do have an efficacious response.***

180. Defendant Budd-Haeberlein's emphasized statements were false because: (a) Non-Carriers exposed to 10mg/kg aducanumab doses did not achieve better clinical outcomes; (b) in Study 302, Carriers exposed to high doses did not experience better clinical outcomes after PV4

than before; (c) Carriers whose treatment or titration was interrupted did not experience worse clinical outcomes than carriers whose treatment and titration were not interrupted; (d) Carriers who received more 10mg/kg aducanumab doses did not experience better clinical outcomes than Carriers who received fewer 10mg/kg doses; and, as a result; (e) Non-Carriers who received 10 milligrams per kilogram did not have an efficacious response; (f) there was no suggestion of a dose response except in one half (Carriers) of one arm (high doses) of one clinical trial (Study 301) of aducanumab's Phase III clinical trials; and (g) Study 302 showed that Study 301 Carriers achieved better results after PV4 because of p-hacking, not aducanumab.

181. Announcing aducanumab's Phase III Topline Results on December 5, 2019, Defendant Budd-Haeberlein stated:

> To summarize, the aducanumab Phase III top line results. Following early termination based on futility, we analyzed a larger dataset. And this showed that in EMERGE, the high dose reduced clinical decline as measured by the primary and secondary endpoints. In ENGAGE, aducanumab did not reduce the clinical decline. ***In a post-hoc analysis, data from a subset of patients exposed to the high dose of aducanumab support the positive findings of EMERGE.***

182. Defendant Budd-Haeberlein's emphasized statements were false because: (a) Non-Carriers exposed to 10mg/kg aducanumab doses did not achieve better clinical outcomes; (b) in Study 302, Carriers exposed to high doses did not experience better clinical outcomes after PV4 than before; (c) Carriers whose treatment including titration was interrupted did not experience worse clinical outcomes than Carriers whose treatment and titration were not interrupted; (d) Carriers who received more 10mg/kg aducanumab doses did not experience better clinical outcomes than Carriers who received fewer 10mg/kg doses; and, as a result (e) the results from ENGAGE (Study 301) did not "support" EMERGE (Study 302) because in Study 302, the subset of Carriers dosed after PV4 did not achieve better outcomes than Carriers dosed before

PV4, thus preventing any conclusions from being drawn; and (f) Study 302 showed that Study 301 Carriers achieved better results after PV4 because of p-hacking, not aducanumab.

183. On an investor call later the same day, December 5, 2019, Defendant Budd-Haeberlein reiterated:

> ***Today, though, we shared a new post hoc analysis, which is what we've called those – that subgroup of individuals who were able to have the opportunity for the intended dosing regimen, the so-called Protocol Version 4 group. And in that subset of patients, aducanumab did support the positive findings of EMERGE and ENGAGE.***

184. Defendant Budd-Haeberlein's emphasized statements were false because: (a) Non-Carriers exposed to 10mg/kg aducanumab doses did not achieve better clinical outcomes; (b) in Study 302, Carriers exposed to high doses did not experience better clinical outcomes after PV4 than before; (c) Carriers whose treatment including titration was interrupted did not experience worse clinical outcomes than Carriers whose treatment and titration were not interrupted; (d) Carriers who received more 10mg/kg aducanumab doses did not experience better clinical outcomes than Carriers who received fewer 10mg/kg doses; and, as a result (e) the results from ENGAGE (Study 301) did not "support" EMERGE (Study 302) because in Study 302, the subset of Carriers dosed after PV4 did not achieve better outcomes than Carriers dosed before PV4, thus preventing any conclusions from being drawn; and (f) Study 302 showed that Study 301 Carriers achieved better results after PV4 because of p-hacking, not aducanumab.

185. On Biogen's earnings call for the fourth quarter of 2019, held on January 30, 2020, Defendant Sandrock stated:

> Final analysis of these data showed that EMERGE was a positive study with the high dose regimen of aducanumab achieving statistical significance on both the pre-specified primary endpoint of CDR Sum of Boxes as well as on all three pre-specified secondary endpoints.

> On the other hand data from the ENGAGE study did not meet the primary endpoint, ***although we do believe that data from patients who achieve sufficient exposure to high dose aducanumab in ENGAGE support the findings of EMERGE***

186. Defendant Budd-Haeberlein's emphasized statements were false because: (a) Non-Carriers exposed to 10mg/kg aducanumab doses did not achieve better clinical outcomes; (b) in Study 302, Carriers exposed to high doses did not experience better clinical outcomes after PV4 than before; (c) Carriers whose treatment including titration was interrupted did not experience worse clinical outcomes than Carriers whose treatment and titration were not interrupted; (d) Carriers who received more 10mg/kg aducanumab doses did not experience better clinical outcomes than Carriers who received fewer 10mg/kg doses; and, as a result (e) the results from ENGAGE (Study 301) did not "support" EMERGE (Study 302) because in Study 302, the subset of Carriers dosed after PV4 did not achieve better outcomes than Carriers dosed before PV4, thus preventing any conclusions from being drawn; (e) there was no suggestion of a dose response except in one half (Carriers) of one arm (high doses) of one clinical trial (Study 301) of aducanumab's Phase III clinical trials; (g) Study 302 showed that the fact that Study 301 Carriers achieved better results after PV4 resulted from p-hacking rather than any relationship.

187. On Biogen's Aducanumab Phase III Topline Results call, held on April 2, 2020, Defendant Budd-Haeberlein stated:

> When we now look at these charts, the top is the pre PV4 population and the bottom is the post-PV4 population. We can see the impact of that protocol amendment. In the pre-PV4 patients, only 21% in EMERGE and 15% in ENGAGE actually had that dark blue, the full possible 14 doses of 10 milligram per kilogram, whereas post that protocol amendment, there is much less heterogeneity and a much larger proportion of subjects, 51% in EMERGE and 47% in ENGAGE, received those full profitable 14 doses.
>
> If we then look at the impact of the population who did have the opportunity to receive the full 14 doses, we should compare the original outcome for both studies, and here, I'm showing the primary endpoint CDR-Sum of boxes for both EMERGE and ENGAGE at Week 78, and you will recall that there was a 23% and a 2%

> difference in those two studies. And if we now look at the patients who had the opportunity for the full 14 doses, in EMERGE, they now have in the high dose a 30% difference versus placebo, and in ENGAGE, where we did not have an outcome in the overall analysis in the PV4 population, the high dose has a 27% difference from placebo. ***And so in these populations a much more similar outcome can be observed.***
>
> * * * * *
>
> So with that, I would like to summarize the aducanumab Phase III top line results. Following study termination based on futility analysis of the larger data set showed that in EMERGE high dose aducanumab did reduce clinical decline as measured by both primary and secondary endpoints. In ENGAGE, however, aducanumab did not reduce clinical de[cline].
>
> ***In a post hoc analysis, data from subs[ets] of patients, the PV4 population who had the opportunity to be exposed to high dose did support the positive findings of EMERGE.*** In sub-studies, aducanumab showed an effect on disease related biomarkers both in CSF and in PET imaging studies[.]

188. Defendant Budd-Haeberlein's emphasized statements were false because: (a) Non-Carriers exposed to 10mg/kg aducanumab doses did not achieve better clinical outcomes; (b) in Study 302, Carriers exposed to high doses did not experience better clinical outcomes after PV4 than before; (c) Carriers whose treatment including titration was interrupted did not experience worse clinical outcomes than Carriers whose treatment and titration were not interrupted; (d) Carriers who received more 10mg/kg aducanumab doses did not experience better clinical outcomes than Carriers who received fewer 10mg/kg doses; and, as a result (e) the results from ENGAGE (Study 301) did not "support" EMERGE (Study 302) because in Study 302, the subset of Carriers dosed after PV4 did not achieve better outcomes than Carriers dosed before PV4, thus preventing any conclusions from being drawn, nor was a "much more similar outcome" observed between Carriers dosed after PV4 in Study 301 and Carriers in Study 302; and (f) Study 302 showed that Study 301 Carriers achieved better results after PV4 because of p-hacking, not aducanumab.

189. On Biogen's earnings call for the second quarter of 2020, held on July 22, 2020, Defendant Vounatsos stated:

> This submission followed ongoing collaboration with the FDA and include data from a comprehensive clinical development program, including EMERGE, the first positive Phase III study ever in this space together ***with supporting data from the Phase III ENGAGE study*** and positive results from the Phase Ib PRIME study. Our data show that aducanumab may help to both reduce the decline of cognitive function and help patients' ability to perform certain activities of daily living, which for some patients may result in independence for a longer period of time.

190. Defendant Vounatsos's emphasized statements were false because: (a) Non-Carriers exposed to 10mg/kg aducanumab doses did not achieve better clinical outcomes; (b) in Study 302, Carriers exposed to high doses did not experience better clinical outcomes after PV4 than before; (c) Carriers whose treatment including titration was interrupted did not experience worse clinical outcomes than Carriers whose treatment and titration were not interrupted; (d) Carriers who received more 10mg/kg aducanumab doses did not experience better clinical outcomes than Carriers who received fewer 10mg/kg doses; and, as a result (e) the results from ENGAGE (Study 301) did not "support" EMERGE (Study 302) because in Study 302, the subset of Carriers dosed after PV4 did not achieve better outcomes than Carriers dosed before PV4, thus preventing any conclusions from being drawn; (f) Study 302 showed that the fact that Study 301 Carriers achieved better results after PV4 resulted from p-hacking rather than any relationship.

191. On the same call, Defendant Sandrock stated:

> I think – look, the filing is based on these 3 studies, EMERGE, ENGAGE and PRIME. EMERGE is the first study to show an effect, not only on the primary endpoint, but all 3 prespecified secondary endpoints. ***We believe that data from ENGAGE – that portions of the data from ENGAGE, a negative study, that portions of it do support the analysis that we did with EMERGE.*** And then I'll say in also PRIME, which was published, shows even though the clinical endpoints were exploratory endpoints, on the highest dose, there was an effect on MMSE as well as CDR sum of boxes. ***And again, very similar that the lower doses did not show much of an effect. So consistent with the findings from ENGAGE and***

> ***EMERGE, you really need to get to the higher dose. And I think our data are all consistent with that.***
>
> * * * * *
>
> So we submitted all the data from those 3 studies that I mentioned: EMERGE, ENGAGE and PRIME. And what the FDA chooses to look at is – that's their purview. ***We – I will say that in terms of the negative study, ENGAGE, we do – we have analyses that show that those who received the highest dose over a sustained period of time do show evidence of efficacy similar to what we found in EMERGE.*** And so that's the data we presented to CTAD and AD/PD, and that's why we believe there's supportive evidence coming from ENGAGE.

192. Defendant Sandrock's emphasized statements were false because: (a) Non-Carriers exposed to 10mg/kg aducanumab doses did not achieve better clinical outcomes; (b) in Study 302, Carriers exposed to high doses did not experience better clinical outcomes after PV4 than before; (c) Carriers whose treatment including titration was interrupted did not experience worse clinical outcomes than Carriers whose treatment and titration were not interrupted; (d) Carriers who received more 10mg/kg aducanumab doses did not experience better clinical outcomes than Carriers who received fewer 10mg/kg doses; and, as a result (e) the results from ENGAGE (Study 301) were not similar to and did not "support" EMERGE (Study 302) because in Study 302, the subset of Carriers dosed after PV4 did not achieve better outcomes than Carriers dosed before PV4, thus preventing any conclusions from being drawn; (f) there was no suggestion that patients who "got to the high dose" did better except in one half (Carriers) of one arm (patients who received high doses) of one clinical trial (Study 301) of aducanumab's Phase III clinical trials; and (g) Study 302 showed that Study 301 Carriers achieved better results after PV4 because of p-hacking, not aducanumab.

193. In Biogen's Aducanumab Phase III Topline Results Presentation at the Alzheimer's Association International Conference (AAIC), held on July 29, 2020, Defendant Budd-Haeberlein stated:

> In the amyloid PET SUVR group, there was a statistically-significant dose and time dependent reduction versus placebo in both low and high-dose. In the CSF sub-study, there was a statistically-significant dose-dependent reduction in phospho-tau and a numerical difference versus placebo in the total tau.
>
> In ENGAGE, the primary and secondary endpoints were not met. There was a numerical difference versus placebo in the low-dose group. In the PET SUVR study, there was a dose and time dependent reduction versus placebo, which was statistically significant.
>
> However, this and the high dose was lower than that, which we've seen in EMERGE and we also understand that the median cumulative dose was lower in ENGAGE subgroup 126 milligram per kilogram versus the EMERGE subgroup at 140 milligram per kilogram.
>
> ***To understand the difference between the studies and the impact of changing the protocol, we defined population by a randomized cohort, who had the opportunity for all 14 doses of 10 milligram per kilogram, and this is termed the post Protocol Version 4 or PV4 population.***
>
> ***If we compare the ITT population with the post-PV4 population, we can see that the post PV4 population in ENGAGE is consistent with the overall ITT population in EMERGE.***

194. Defendant Budd-Haeberlein's emphasized statements were false because: (a) Non-Carriers exposed to 10mg/kg aducanumab doses did not achieve better clinical outcomes; (b) in Study 302, Carriers exposed to high doses did not experience better clinical outcomes after PV4 than before; (c) Carriers whose treatment or titration was interrupted did not experience worse clinical outcomes than Carriers whose treatment and titration were not interrupted; (d) Carriers who received more 10mg/kg aducanumab doses did not experience better clinical outcomes than Carriers who received fewer 10mg/kg doses; and, as a result (e) the results from ENGAGE (Study 301) are not consistent with EMERGE (Study 302) because in Study 302, the subset of Carriers dosed after PV4 did not achieve better outcomes than Carriers dosed before PV4, thus preventing any conclusions from being drawn; and (f) Study 302 showed that Study 301 Carriers achieved better results after PV4 because of p-hacking, not aducanumab.

195. In Biogen's Phase III Topline Results Presentation at the 23rd Chinese National Conference of Neurology, held on September 19, 2020, Defendant Budd-Haeberlein stated:

> So to go back to the primary results and the primary endpoint for both EMERGE and ENGAGE, as I showed you earlier, CDR Sum of Boxes in the high dose group was 22% difference from placebo in EMERGE and a 2% difference in ENGAGE. If we now look at the post-PV4 population, we have a minus 30% effect in the post-PV4 population in CDR Sum of Boxes in EMERGE and a minus 27% difference from placebo in the ENGAGE population. So essentially in EMERGE, the signal remains whereas in ENGAGE, there was no previous signal. However, when patients had the full opportunity for the 14 doses of 10 milligram per kilogram, we do identify a difference from placebo. And here are the line charts of those populations.
>
> ***So in summary, following study termination based on futility, there was an analysis of a larger data set. In EMERGE, the high dose aducanumab reduced clinical decline as measured by both the primary and secondary endpoints. In ENGAGE, aducanumab did not reduce the clinical decline. However, in a post-hoc analysis, data from a subset of patients exposed to high dose aducanumab support the positive findings of EMERGE***. In sub-studies, aducanumab also showed an effect on disease-related biomarkers.

196. Defendant Budd-Haeberlein's emphasized statements were false because: (a) Non-Carriers exposed to 10mg/kg aducanumab doses did not achieve better clinical outcomes; (b) in Study 302, Carriers exposed to high doses did not experience better clinical outcomes after PV4 than before; (c) Carriers whose treatment or titration was interrupted did not experience worse clinical outcomes than Carriers whose treatment and titration were not interrupted; (d) Carriers who received more 10mg/kg aducanumab doses did not experience better clinical outcomes than Carriers who received fewer 10mg/kg doses; and, as a result (e) the results from ENGAGE (Study 301) did not "support" EMERGE (Study 302) because in Study 302, the subset of Carriers dosed after PV4 did not achieve better outcomes than Carriers dosed before PV4, thus preventing any conclusions from being drawn; and (f) Study 302 showed that Study 301 Carriers achieved better results after PV4 because of p-hacking, not aducanumab.

B. Defendants Falsely Told Investors That the Reductions In Amyloid Plaque Caused Better Clinical Outcomes

i. Defendants Falsely Asserted that Study 301 and Study 302 Showed that Decreases In Amyloid Plaque Were Correlated To Better Clinical Outcomes

197. Studies have not shown that removing amyloid plaque has any impact on Alzheimer's disease sufferers' clinical outcomes.

198. As Dr. Ronald C. Petersen, who directs the Mayo Clinic's Alzheimer's Disease Research Center and its Study of Aging (both focusing on neuroimaging and biomarkers) explained in a December 5, 2019 *Washington Post* article:

> ***The million-dollar question in the field has always been, "So what?" If you remove plaque — the insoluble form of amyloid — at this stage of the disease, does it make any difference? Or is that sort of the tombstone of the disease?***

199. Biogen claimed the interim Phase I aducanumab clinical trial (Study 103) results showed a correlation between removal of amyloid plaque and better clinical outcomes. The results sparked excitement in both the medical and investor communities, because it suggested that aducanumab's mechanism of action might actually ***work***:

a. A Barclays analyst wrote in a January 26, 2018 report:

> Positive aducanumab outlook driven by two factors: Our positive outlook for aducanumab is driven by two general factors we believe distinguish it from many of the other unsuccessful anti-AB antibodies:
>
> * * * * *
>
> (2) Long-term, dose-dependent positive efficacy and safety data. At CTAD last year, Biogen presented long-term follow-up Phase 1b aducanumab data, including 36 months results from the fixed-dose cohort and 24-month results from the titration cohort. Overall, across both data sets, there was a decline in the amyloid plaque levels in a time and dose-dependent manner; there was also a similar response with regards to the rate of cognitive decline as measured by the CDR-SB and the MMSE.

b. A J.P. Morgan analyst wrote in a February 22, 2019 report about a conference call the analyst held with two leaders in the field. The analyst reported that the Director of the Cleveland Clinic Center for Brain Health was excited about aducanumab because: "The PRIME

data is the first time we saw a directional concordance in amyloid reduction and clinical endpoints; before you saw slight improvements in cognition but nothing on biomarkers or vice versa."

200. The FDA, likewise, focused Defendants' attention (and was itself focused) on whether there was a correlation between amyloid plaque removal and clinical outcomes. In the June 2019 Meeting (as set out by its minutes), the FDA asked Biogen to analyze whether there was a correlation between biomarker results and clinical outcomes in Study 301 and 302 results before the Class Period even started:

> We encourage you to explore the relationship between exposure (e.g. dose, and aducanumab concentration), amyloid positron emission tomography standard uptake value ratios ["PET SUVR", a metric showing amyloid reduction], and clinical endpoints.

201. Biogen conducted a substudy within aducanumab's Phase III trials that measured patients' level of amyloid plaque through PET SUVR.[18] The substudy had two aims: to determine whether aducanumab reduced the amount of amyloid plaque and to determine whether reductions in amyloid plaque correlated with positive clinical outcomes. 540 Patients from Study 301, and 442 from Study 302, participated in the amyloid plaque PET substudy. Biogen collected week 78 biomarker and clinical outcome data on about two-thirds of these patients.

202. Defendants disclosed the existence of the substudy and asserted that its results were positive. But though they had disclosed similar detailed results when they announced Study 103's interim findings, they did not disclose the substudy's results.

203. Defendants' statements were false. The substudy showed that there was ***no*** correlation between amyloid plaque reduction and clinical outcomes.

[18] Biogen also conducted substudies to examine whether aducanumab had effects on other biomarkers but the number of patients studied – 36 – made any conclusions mere speculation.

204. The correlation coefficient is the principal measure of the relationship between two variables. The coefficient is a number between -1 and 1. A correlation coefficient of 1 means that for every positive increase in one variable, there is an increase of a fixed proportion in the other. A correlation coefficient of -1 means that for every positive increased in one variable, there is a decrease of a fixed proportion in the other. A correlation coefficient of 0 means there is no relationship between the two.

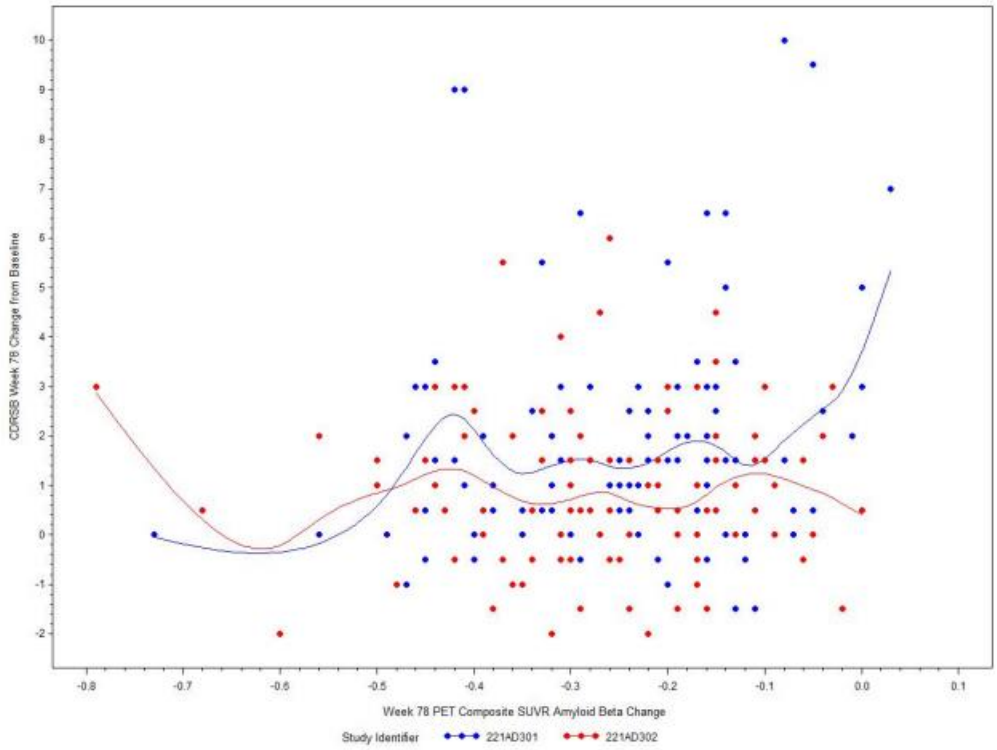
205. Statisticians use the square of the correlation coefficient (R^2) to measure the proportion of the change in one variable that is explained by the other. Technically, R^2 measures the proportion of the variance explained by one variable.

206. In the high dose group, neither the correlation coefficient nor R^2 showed a meaningful relationship between amyloid beta levels and positive clinical outcomes. In fact, the correlation coefficient in Study 302 – the successful study – showed that patients who lost more amyloid plaque did slightly worse:

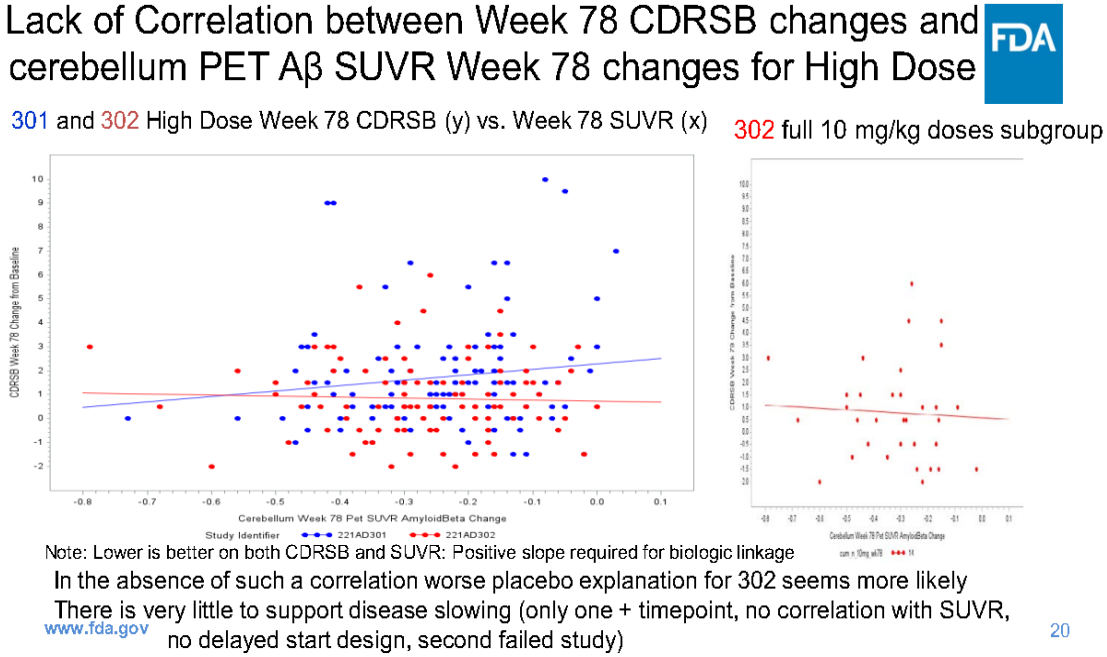
	Study 301	Study 302	Pooled (approximately)
Correlation coefficient between amyloid beta levels and CDR-SB	0.135	-0.036	0.084
Proportion of variation in clinical outcomes explained by changes in biomarkers (R^2)	1.82%	0.13%	0.71%

207. A graph comparing patients' amyloid PET SUVR against their CDR-SB scores shows no relationships:

Figure 18. Assessing Correlation of Amyloid Pet and CDRSB in High Dose at Week 78



208. Limiting the analysis to patients who received the full fourteen 10mg/kg doses only increases the negative correlation:



209. As Massie noted in the Draft Massie Report:

> Why don't high dose non-carriers show a clinical effect in Study 302 if they got 10mg/kg earlier, have less ARIA dose reductions and ***if they showed a bigger effect on cerebellum SUVR AB uptake? This seems to call into question whether AB PET SUVR in cerebellum is a surrogate. In fact, within the high dose group, there is actually no correlation between Week 78 change in cerebellum SUVR AB and Week 78 change in CDRSM [sic]. This seems to call into question a disease slowing claim.***

210. Thus, the data Defendants concealed shows that aducanumab's positive clinical outcomes are not caused by the removal of amyloid plaque. Rather, the data show that the amyloid hypothesis ***is not true.*** Removing amyloid plaque does not improve clinical outcomes and aducanumab does not work by removing amyloid plaque. As Dr. Jonathan P. Jarrow, a surgical oncologist who worked in senior positions at the FDA from 2010 through 2019, explained in a conversation with a UBS analyst reported in a December 4, 2020 UBS report:

> In the vote that was unanimously kind of positive about effecting [accelerated approval], the pharmacodynamics process of Alzheimer's disease, the caveat was it affected the biomarker, it didn't affect the outcome of the disease. ***Therefore, the biomarker isn't the surrogate, and that perhaps the field should abandon this as a marker for the disease.*** That didn't get translated into some of the press releases that I have seen, and it's been translated into a win. ***So, if, if you really listen to what the Advisory Committee said, they said, you can't use an accelerated approval using a surrogate, because this isn't a surrogate yet. Even though it clearly affected the biomarker, the biomarker had no correlation with the clinical outcome.***

ii. Defendants Succeeded in Misleading Investors That There Was A Correlation Between Amyloid Plaque Removal and Clinical Outcomes

211. Defendants' misstatements and omissions of material fact succeeded in misleading investors, as the following statements from analysts and doctors show:

a. Dr. Petersen was quoted in a December 5, 2019 Washington Post article as saying:

> The million-dollar question in the field has always been, "So what?" If you remove plaque — the insoluble form of amyloid — at this stage of the disease, does it make any difference? Or is that sort of the tombstone of the disease? ***This [aducanumab results] seems to imply that removing the amyloid even at this stage can have a clinical impact.***

b. In an October 29, 2019 report, an RBC analyst noted that "***Internal consistency helps strengthen case for EMERGE being a legitimate [positive] study***: PET biomarker of amyloid also consistent" above a graph showing a biomarker dose response in the EMERGE study.

c. In a December 5, 2019 report, a Credit Suisse analyst related comments made by a doctor with whom the analyst had held a conference call that "in [the doctor's] view, data from the EMERGE trial displayed a meaningful clinical benefit that was correlated with biomarkers."

d. In a December 5, 2019 report, a BTIG analyst wrote that:

> The company reiterated the point we feel is most illuminating: ***plaque removal in ENGAGE was incomplete (Exhibit 2). We thought the arguments went a long way to help the discussants dismiss the ENGAGE trial and look for positive segments of the data sets based on full doses.***

e. In a December 5, 2019 report, an Oppenheimer analyst wrote that "[t]he favorable clinical results from EMERGE are entirely consistent with dose-dependent changes in key biomarkers including amyloid PET SUVR[.]"

f. In a December 23, 2019 report, an SVB Leerink analyst wrote that a biostatistician with whom they had held a conference call "suggested that the positive association between target reduction (amyloid PET scan and CSF biomarkers) and clinical response in EMERGE would then enable the positive biomarker effect in ENGAGE to be used to support the application."

g. In a February 3, 2020 report, an SVB Leerink analyst reported that they had surveyed physicians, and that in these physicians' views:

- Physicians think the dose-dependent and significant Abeta/p-Tau reductions are in line with aducanumab's clinical efficacy data.

h. Expressing their own views in the same report, the analysts concluded that the "hook" for aducanumab was its proof of a "[c]lear dose response in Abeta reduction and disease

modification effect." The report continued with a header on page 22: "Treatment effect of aducanumab was well correlated with biomarker changes (Abeta and Tau), providing additional data supportive of disease modification." The report concluded that aducanumab was approvable because "[p]ositive association between target reduction (amyloid PET scan and CSF biomarkers) and clinical response should support the use of biomarker data from both trials as additional evidence."

i. In an October 13, 2020 report, the same analyst wrote that:

> We believe aducanumab could be the 1st [disease modifying therapy] approved for treating Alzheimer's, and that it would not require an additional trial because…
>
> []
>
> Aducanumab showed a clear dose-response ***and a consistent association between Abeta/Tau biomarker reduction (dose-dependent imaging results) and clinical response of slowing cognitive decline*** in all completed trials[.]

j. In a November 3, 2020 report, a Wells Fargo analyst wrote:

> ***EMERGE appears as less of an outlier on demonstrating strong correlation between reduction AB PET SUVR and improvements in cognition as measured by CDR-SB and other secondary measures***, and the outlier result, requiring explanation may be the failure of ENGAGE to demonstrate improvements in CDR-SB despite statistically significant effect on AB PET SUVR.

212. Indeed, Defendants understood that they risked misleading investors. On the December 5, 2019 Q&A, one analyst asked for specific data on the correlation between amyloid plaque biomarkers and clinical outcomes in Study 301 and 302. The analyst pointed out that Biogen had previously produced such analyses for Study 103. Defendants acknowledged that the analyst's question was "very important" but did not provide the information. Instead, they misleadingly pointed to Study 103 data which had found a correlation, knowing that Study 301 and 302 had shown no such relationship:

> Q: Just maybe first, I know in the PRIME data, you had looked at the relationship between plaque reduction and, I think, CDR and both MMSE [two clinical outcome measures] and

> reported that you saw a moderate correlation there, I think, on a Spearman analysis. If you plot the plaque reduction data from the current Phase IIIs and you look at that irrespective of dose versus CDR, I just wonder if you see a similar correlation.
>
> Defendant Haeberlein:
> [Analyst], thanks for the question. ***And it's obviously a very important one.*** We're really limiting our responses today to the analysis that we have shared this morning.
>
> Defendant Sandrock:
> Yes. And [analyst], you're right. In PRIME, when we looked at people [who] had less than one standard deviation change in amyloid plaque versus those that had greater than one standard deviation change, those who had less than one standard deviation change, as published, did not have a clinical benefit, whereas those who had greater than one standard deviation change did. ***And so in that study, we did see that correlation referred to.***

iii. Defendants Manipulate the Statistical Analysis Plans For Study 301 and 302 To Manufacture A Correlation

213. The FDA initially required that Biogen prepare a "prospectively-specified statistical analysis plan" for its analysis of correlations between biomarkers and clinical outcomes. The minutes of the December 2014 meeting between Biogen and the FDA provide:

> We have no objection to the use of the secondary clinical and biomarker efficacy endpoints that you have proposed for your Phase 3 trials. However, should you wish to include results that are based on the analysis of those measures in the Prescribing Information for [aducanumab], the following criteria should be satisfied:
> []
>
> - The ***prospectively-specified*** statistical analysis plan for those secondary efficacy measures should include methods for preserving the Type I error, as appropriate.
>
> * * * * *
>
> [Y]ou should ***pre-specify*** a separate detailed statistical plan for the outcome measure that is to be derived from brain amyloid imaging, as well as for every other biomarker-derived outcome evidence[.]

214. On or about June 22, 2021, the FDA published a final version of the Massie Report that had been shared internally in connection with the aducanumab approval decision ("Final Massie Report").

215. The Draft Massie Report had noted that the aducanumab biomarker Phase III trials' Statistical Analysis Plan was dated in 2020 ("Unblinded Statistical Analysis Plan"). In that report, Massie expressed surprise at the date because statistical analysis plans must be prepared before the analysis is conducted. In 2020, Biogen already had access to every patient's individual data from the trials. It could thus manipulate the Unblinded Statistical Analysis Plan to produce whatever result it wanted.

216. The Final Massie Report disclosed that there had been an earlier biomarker Statistical Analysis Plan.

217. Biogen formulated a statistical analysis plan on September 12, 2018, before unblinding ("Blinded Statistical Analysis Plan"). When Biogen formulated the Blinded Statistical Analysis Plan, it did not have the benefit of knowing any data. It was thus impossible for Biogen to formulate a Blinded Statistical Analysis Plan that it knew it could meet.

218. The Unblinded and Blinded Statistical Analysis Plans called for Biogen to conduct the same statistical tests to determine whether there was a correlation between clinical outcomes and amyloid beta levels. But while the Blinded Statistical Analysis Plan called for separate tests to be conducted separately on each group (placebo, low dose, and high dose), the Unblinded Statistical Analysis Plan called for Biogen to combine the low dose and high dose groups of the two studies when conducting statistical tests.

219. On its face, the amendment to the Blinded Statistical Analysis Plan made no sense. Biogen revived the aducanumab BLA because, it claimed, the data showed that those patients that received a sufficient number of high doses (10 mg/kg) showed efficacy. Thus, when conducting analyses, Biogen carefully separated out the high dose group from other dosages to claim that

aducanumab had an effect in the high dose group. Further, Defendants claimed that lower doses were simply not effective.

220. But modifying the Statistical Analysis Plan let Biogen conclude that the test was successful. Defendants knew there was no correlation between clinical outcomes and biomarkers in the high dose groups. Further, for the crucial Study 302 high dose group, the correlation between clinical outcomes and biomarkers in high-dose patients was actually negative. But Biogen observed an anomalously high relationship between biomarkers and clinical outcomes in one group: low dose Study 302 patients. By pooling low dose and high dose patients, Biogen manufactured an apparent correlation between clinical outcomes and biomarker in the all-important Study 302:

Correlation coefficient between amyloid beta levels and clinical outcomes	Low dose	High dose	Pooled
Study 301	0.009	0.135	0.026
Study 302	0.165	-0.036	0.105
Pooled	0.083	0.084	0.066

iv. Defendants' Specific False Statements About Correlation Between Amyloid Plaque and Better Clinical Outcomes

221. On the October 22, 2019 call, Defendant Vounatsos stated:

> [T]he new analysis of the larger dataset, which was conducted in consultation with the FDA, showed that aducanumab had a dose-dependent effect ***on the underlying pathology as measured by amyloid-PET imaging and reduced clinical decline in patients with early Alzheimer's disease*** as measured by the pre-specified primary and secondary endpoints.

222. Defendant Vounatsos's statement was misleading because: (a) there was no correlation between removal of amyloid plaque and clinical outcomes; (b) in the high-dose arm of Study 302, there was a slight negative relationship between removal of amyloid plaque and

clinical outcomes; and therefore (c) even if there had been any reduction[19] in clinical decline in patients with early Alzheimer's disease, the reduction would have been unconnected to the reduction in amyloid.

223. On that same call, Defendants Sandrock and Budd-Haeberlein stated:

> Q: Great, thanks for taking the question. I guess a follow-up and sort of second question from me. So first one is, you've been talking about exposure and dose a lot. Could you just broadly comment on how many of these patients actually achieved all the factors that you were looking for and how easily you think that will be the case in clinical practice. And I guess, the related question to that is, this dose exposure curve that you're sort of talking about [Sandrock]. I mean, were there characteristics that were different where the kinetics of the amyloid plaque reduction different in these subgroup of patients with the achievement of tau or amyloid reductions were they significantly different? I'm wondering what you think is sort of biologically happening to account for this steep dose exposure curve (inaudible)?
>
> **Defendant Sandrock**: These are good questions Matthew and we're still learning as we look at the data, but I would say this, the – even in MCI patient, if you look at the amount of amyloid in the brain, it's tremendous. It took 20 years to build that much up and in the context of an 18-month trial, you have to remove a large amount of amyloid. I think that's what distinguishes aducanumab and BAN2401, is that we can – it's safe enough to achieve the doses that allow us to remove a large amount of amyloid. ***And if you don't remove a large amount, you're not going to get an effect.*** Also there is a lag. ***You remove amyloid, and then there is a little bit of a lag for the clinical effect.*** We saw that in PRIME for example, where we did have some amyloid lowering at six months, but we saw no difference in the clinical outcomes at six months. It was – it took the 12-month time period to see – to start to see an effect on clinical outcomes.
>
> ***So, in addition to a large amount of amyloid removal, I think you need to have a little bit of time for that, for that biological activity to have an effect on clinical outcomes. That's what we see and I would say that if you look at the amyloid-PET results that was on one of the slides and those who had more than 10 doses of 10 milligrams, you can see that the SUVR score is very similar in ENGAGE in that subgroup of patients in ENGAGE to the EMERGE total dataset. So – and so again, what it says is that if you give enough of the high dose, you can achieve a certain amount of amyloid removal and that certain amount is what's required to see the reduction in clinical decline in an 18-month study.***

[19] As set out in Paragraphs 148-168, aducanumab did not show a dose-dependent effect on clinical outcomes.

> **Defendant Budd-Haeberlein:**
> Yes, [Sandrock] just to add to that, on the question of numbers. On the graph that you've just referred to, you got the end numbers. So they were 147 for EMERGE and 116 for ENGAGE in that CDR-Sum of Boxes analysis. But the question you ask of how many patients have the precise criteria? Well there aren't precise criteria. Dose response is not binary. ***And so, given the levels of dose you have a different response and it's a bit of a sliding scale. So we have that exploratory analysis that we disclosed to explain what it is we learned around the importance of dose, but there is no perfect number of doses that are required, it's not binary.***

224. Defendants Budd-Haeberlein and Sandrock's emphasized statements were misleading because: (a) there was no correlation between removal of amyloid plaque and clinical outcomes; (b) in the high-dose arm of Study 302, there was a slight negative relationship between removal of amyloid plaque and clinical outcomes; and therefore (c) there was no clinical effect following removal of amyloid plaque; (d) amyloid plaque removal in Study 302 did not explain better clinical outcomes than in Study 301; (e) as there was no correlation between amyloid plaque removal and clinical outcomes, Defendant Sandrock's statement that "***you can achieve a certain amount of amyloid removal and that certain amount is what's required to see the reduction in clinical decline in an 18-month study"*** was not true; and (f) even if there had been any reduction in clinical decline in patients with early Alzheimer's disease, the reduction would have been unconnected to the reduction in amyloid.

225. On the same call, Defendant Budd-Haeberlein stated that the difference in plaque reduction "tell[s] the same narrative" as the clinical outcomes:

> Q: Within the high dose arm in the ENGAGE study, can you talk about the magnitude of plaque reductions you observed in patients who titrated all the way up to the highest dose versus patients who were stopped at 6mg/kg and I guess, ***does the – does a differential magnitude of plaque reduction in those patients at all tell the same narrative you're seeing on the difference in clinical outcomes?*** []
>
> Defendant Budd-Haeberlein: [] So to your first question in amyloid plaque reduction, we do believe that PET measurement of amyloid plaque reduction is a very sensitive tool of dose and ***you've correctly identified that ENGAGE at the high dose is showing a lower***

> ***reduction than in EMERGE and we do believe that that is a clear reflection of the lower doses that were achieved in that high-dosing group in ENGAGE.***

226. Defendants Budd-Haeberlein's emphasized statements were misleading because: (a) there was no correlation between removal of amyloid plaque and clinical outcomes; (b) in the high-dose arm of Study 302, there was a slight negative relationship between removal of amyloid plaque and clinical outcomes; and therefore (c) the differences between Study 301 and Study 302 amyloid plaque removal does not support a narrative that lower amyloid plaque removal in Study 301 caused its failure because in Study 302, patients who saw higher amyloid plaque removal experienced worse clinical outcomes; and (d) Study 301's worse clinical outcomes and worse amyloid plaque removal compared to Study 302 are not connected, rather than a "clear reflection" of the same trend.

227. On October 23, 2019, Defendant Vounatsos was interviewed on MSNBC. On that interview, Defendant Vounatsos directly stated that the decrease in amyloid plaque "leads to" better clinical outcomes:

> Q: So [aducanumab] is a monoclonal antibody that actually is designed to go after beta-amyloid plaques which are seen in some Alzheimer's patients. You're telling me that it actually removes the plaques. ***There was some speculation that maybe that's not it; could be that you get Alzheimer's and the plaques then come about as a result of Alzheimer's, it's not an actual cause.*** You're convinced beta-amyloid is the key to dealing with –
> Defendant Vounatsos: More than ever. ***What we demonstrate is that [aducanumab] who's binding to the right part of the amyloid-beta, the aggregated form of amyloid-beta, is able to erode and eliminate the plaque leading to the benefits we see in terms of cognition for the patients. It reduces basically the decline and we can see effects such as on memory orientation, language, but also functionally the ability to take care of oneself.***

228. Defendant Vounatsos's emphasized statements on the October 23, 2019 interview was false because (a) there was no correlation between removal of amyloid plaque; (b) in the high-dose arm of Study 302, there was a slight negative relationship between removal of amyloid plaque and clinical outcomes; and therefore (c) the reduction in amyloid plaque did not "lead[]

to" the clinical benefits; and (d) aducanumab's Phase III trials did not demonstrate that the reduction of plaques was an "actual cause" of clinical outcomes.

229. On the December 5, 2019, Q&A, Defendants explained the discrepant results between Study 301 and Study 302 by claiming that Study 302 was positive ***because*** more plaque was removed than in Study 301:

> Q: Congrats on the presentation today. So I have a question on the amyloid reduction. How do you think about the amyloid reduction in both trials looking similar yet really yielding different results? And how does this square with your hypothesis that there was a sufficient difference in the trial with – in relation to the protocol amendment – to drive a divergent result?
>
> Defendant Sandrock: So I'll start. And I'm sure [Budd-Haeberlein] will have things to add. But I would point out that in the high – in the low-dose group, the reduction was similar between EMERGE and ENGAGE. But in the high-dose group, there was actually a difference. And in fact, [Budd-Haeberlein] pointed out the SUVR numbers. Even though the amyloid PET was done in a sub-study, it is such a precise measurement. If you look at the error bars, they're tiny, they almost blend right into the actual symbol. And so the small differences between – ***the difference between EMERGE and ENGAGE actually is significant. And I think [Budd-Haeberlein] pointed out this morning that in the EMERGE trial, the reduction was what we had expected based on the PRIME data. But ENGAGE fell short. And that's the reason why we started to focus on exposure because it looked like the amyloid reduction in ENGAGE was not quite what we had expected. And that's what led us down this track of looking at drug exposure.***
>
> Defendant Budd-Haeberlein: Yes, nothing to add. Thanks, [Sandrock].

230. Defendant Sandrock's emphasized statements, and Defendant Budd-Haeberlein's endorsement thereof, were false and misleading because: (a) there was no correlation between removal of amyloid plaque and clinical outcomes; (b) in the high-dose arm of Study 302, there was a slight negative relationship between removal of amyloid plaque and clinical outcomes; (c) while amyloid plaque removal and clinical outcomes were correlated in Study 103 (PRIME), they were not correlated in Study 302 (EMERGE); and therefore (d) Study 301's worse clinical outcomes and worse amyloid plaque removal against Study 302 are not connected; and (e) Study 302's results were not similar to Study 103's.

231. Defendant Sandrock further falsely told an analyst employed by Credit Suisse that differences in levels of plaque removal explained the discordant results between Study 301 and 302 and between pre- and post-PV4, as reported in a December 3, 2019 analyst report:

> ***As part of an explanation for the negative ENGAGE results, [Defendant] Sandrock indicated to us that the amyloid lowering effect in ENGAGE underperformed expectations. He believes that the effect may have been partly responsible for the confounding results (e.g. due to less target engagement).*** He also said that later enrollers had a different effect than early enrollers.

232. Defendant Sandrock's emphasized statements, and Defendant Budd-Haeberlein's endorsement thereof, were false and misleading because: (a) there was no correlation between removal of amyloid plaque and clinical outcomes; (b) in the high-dose arm of Study 302, there was a slight negative relationship between removal of amyloid plaque and clinical outcomes; (c) while amyloid plaque removal and clinical outcomes were correlated in Study 103 (PRIME), they were not correlated in Study 302 (EMERGE); and therefore (d) Study 301's worse clinical outcomes and worse amyloid plaque removal against Study 302 are not connected.

C. Defendants Misleadingly Suggested That Regional Variation Was Not Important

233. Alzheimer's disease is notoriously protean. It symptoms vary from patient to patient, from culture to culture, and from country to country.

234. Determining CDR-SB scores is subjective. CDR-SB scores are evaluated through semi-structured interviews. Professionally trained interviewers ask patients about their difficulties in six domains (memory, orientation, judgment and problem solving, community involvement, homes and hobbies, and personal care), in the presence of a caregiver. The interviewer assigns a severity scores of 0-3 in each domain for a total potential score of 0 to 18.

235. Regional or cultural variations may cause patients or caregivers to answer questions, or interviewers to rate responses, differently – particularly as many patients were effectively unblinded by ARIA events.

236. Thus, investors were attentive to any regional variations in the results aducanumab achieved.

237. Before the start of the Class Period, the FDA asked Defendants to examine aducanumab's clinical trial results to determine whether demographic or other factors might explain clinical trial outcomes. The FDA asked Biogen in preparation for the June 2019 Meeting:

> Have you explored whether differences in demographic and other baseline characteristics, other than those outlined in Table 6 in your meeting package, may explain the differences in the final efficacy analyses high dose groups of Study 221AD301 and Study 221AD302? The meeting package states that there are no major demographic or baseline differences between study arms within each study. We are curious about whether there may be demographic or baseline differences between studies that contribute to the different results in the high dose group of each study.

238. In the December 5, 2019 Q&A, Defendant Budd Haeberlin claimed that neither geography nor demographics explained trial results:

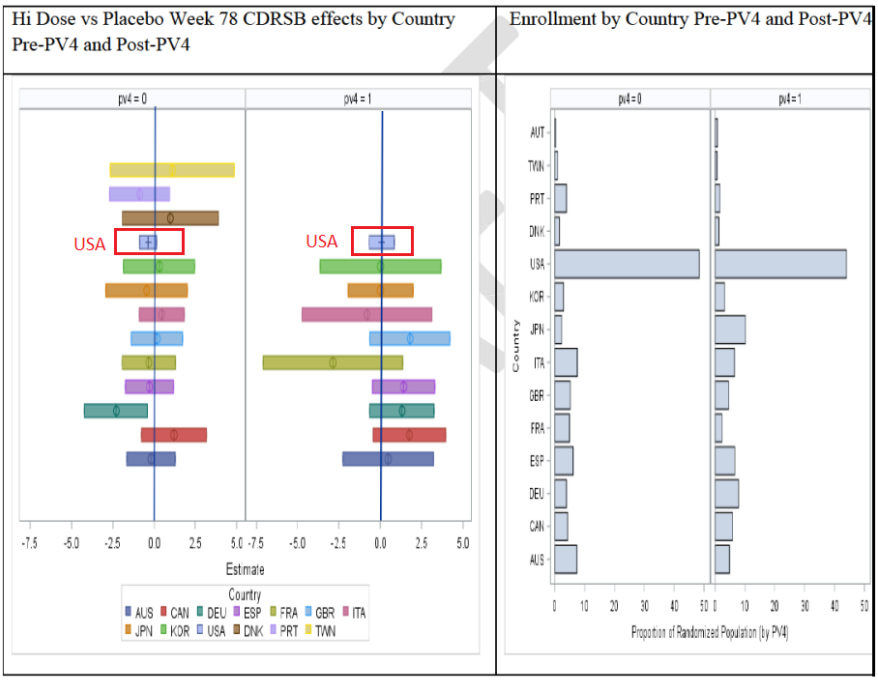
> Q: [] And related to that, are you certain that there isn't anything related to study sites, geography, or any other variation that could explain the breadth of the improvement other than just the exposure?
>
> Defendant Budd-Haeberlein: [] And to the second part of your question***, we believe, having looked very closely at the baseline demographics and characteristics, that none of these are driving the overall outcomes that we see or the differences that we see between the studies.***

239. Defendant Budd-Haeberlein's statements were misleading because, as set out immediately below: (a) there were wide differences between clinical outcomes by country; (b) U.S. patients' clinical outcomes were worse than the global average; (c) in Study 301 in the U.S., post-PV4 patients' clinical outcomes were no better than placebo; and, therefore, (d) regional variations showed that aducanumab was not effective as to the U.S. population.

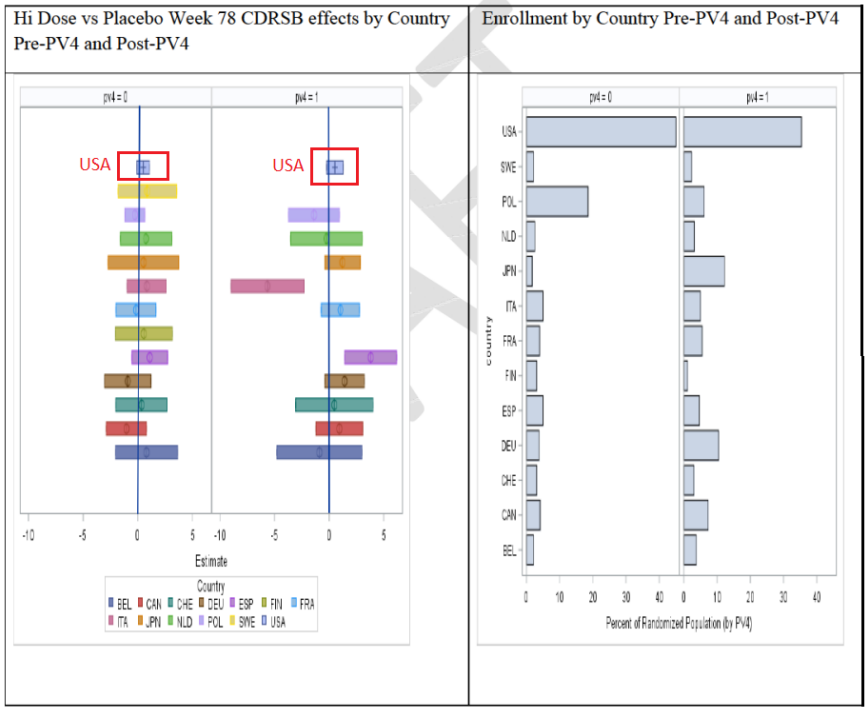
240. Defendants concealed country-by-country and region-by-region data from the public. Aducanumab's Phase III clinical trials took place in 20 countries. There were statistically significant differences between countries in the effect of aducanumab in both Study 301 (p-value <0.0001) and Study 302 (p-value <0.0001).

241. Further, the data showed the U.S. performed significantly worse than average. The U.S. accounted for 46.3% and 39.8% of the patient population of Study 301 and Study 302, respectively.

242. In Study 301, U.S. patients who received a high dose did worse than placebo before PV4 and nearly identically thereafter:



243. The treatment effect in Study 302 was marginal both before and after PV4:



244. In the United States, on average, clinical outcomes for patients with the high dose were 0.19 CDR-SB points better than placebo (or about 20% less than the global average result).

245. Because results vary by country, U.S. patients' poor response was a serious cause for concern.

246. Similarly, though aducanumab is meant to be used early in Alzheimer's progression, the only age group whose performance was statistically significantly better than placebo were the over 75 (0.4521 points on the CDR-SB scale). The clinical outcomes for the subgroup of patients aged 65 or younger who received high doses of aducanumab were worse than placebo (-0.05546 points). In Study 302, the effect on clinical outcomes for prodromal (early stage) patients were worse (0.303 points) than those on patients who had more advanced mild dementia (1.013 points).

D. Defendants Misleadingly Concealed Data Showing the Secondary Endpoints Did Not Support Clinical Trial Results

i. Defendants Conceal That all Endpoints Were Correlated

247. Defendants claimed that the fact that Study 302 was positive on all endpoints, rather than just its primary endpoint, gave further confidence that aducanumab worked.

248. For example, on the December 5, 2019 Q&A, Defendant Budd-Haeberlein claimed that the "breadth" of endpoints having an effect was "encouraging":

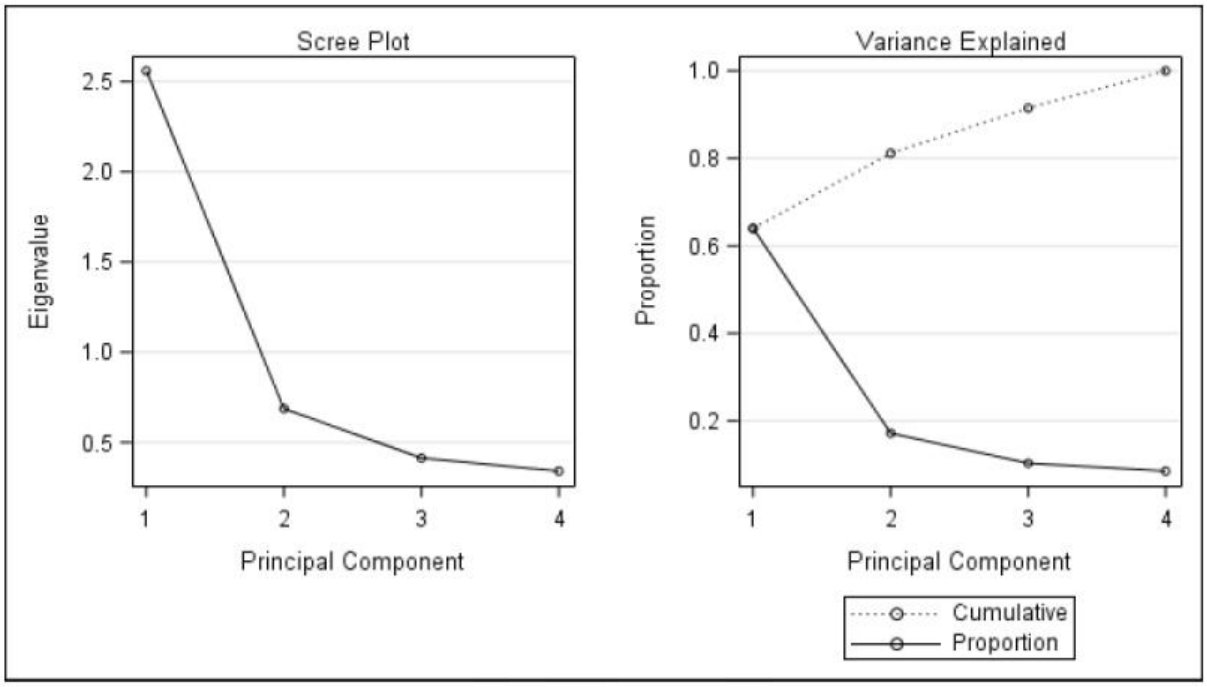
> Q: Congrats on the results. The panel discussion seems pretty intrigued by the functional endpoint. So could you maybe talk about the consistency of the results across various components? Was there any particular component that was driving the delta? Then can you also talk about how the functional endpoints trended in both the studies – specifically after the patients – after you implemented the full commitment – the Protocol 4 commitment?
>
> Defendant Budd-Haeberlein: Yes, I'll take the last bit first. We didn't show the secondaries, including the functional endpoint for the Protocol Version 4 population. But the outcomes on those endpoints were consistent for that population. We haven't disclosed the pieces of those endpoints. One thing I would like to say is if you take a look at EMERGE, the primary endpoint, CDR sum of boxes, is comprised of both cognitive and functional components, 3 pieces each. Then the others, MMSE and ADAS-Cog, are more cognitive tests. Then you've got ADCS-ADL, which is a functional score. ***So it's the breadth of endpoints having on effect on each of these, which is encouraging rather than any one of them or pieces thereof.***

249. That Study 302 was positive on all endpoints is not meaningful because, as shown by the data Defendants concealed, the endpoints are not independent of each other. Rather, scores on all the endpoints are closely correlated. In Study 302, patients who experienced good clinical outcomes as measured by CDR-SB also experienced good clinical outcomes as measured by MMSE, ADAS-Cog 13, and ADCS-ADL-MCI:

Correlation Coefficients				
	CDRSB	MMSE	ADAS-cog	ADCS-ADL-MCI
CDRSB	1.00000	-0.55312	0.49447	-0.64083
MMSE	-0.55312	1.00000	-0.58233	0.44297
ADAS-cog	0.49447	-0.58233	1.00000	-0.39773
ADCS-ADL-MCI	-0.64083	0.44297	-0.39773	1.00000

250. Statisticians also use a technique called principal component analysis to determine how many dependent variables are necessary to interpret the results, which they can then plot on scree plots. Here, as the Draft Massie Report noted, "because [the scree plot] levels off very quickly [], it suggests that, rather than four independent factors, one or at most two are needed to explain the variation among the four key endpoints. Therefore, again, the four key endpoints do not measure very distinct efficacy information, i.e. one or at most 2 captures the key information."

Figure 32 Scree Plot of Principal Components of Primary and Key Secondary Endpoints



251. Thus, that aducanumab had statistically significant results on all four endpoints in Study 302 says nothing about whether it was effective. Rather, the concealed data shows that Study 302 did well on all endpoints because they measure the same thing.

252. Yet in a December 23, 2019 report, an SVB Leerink analyst reported on a conference call with an expert biostatistician, who was encouraged that "EMERGE Showed a strong signal with a positive dose-dependent response across all four independent endpoints that have low correlations."

ii. The Data Defendants Obtained Before Unblinding Did Not Show that Secondary Endpoints Were Statistically Significant

253. As set out above, Biogen argued that the secondary endpoints showed statistically significant positive results and thus supported approval. The FDA cited this fact in approving aducanumab.

254. Biogen initially presented a patient-level data set to the FDA at June 2019 meeting. The data set was collected when Biogen was blinded.

255. Biogen later filed with the FDA a data set in support of its BLA. The data set was collected after Biogen was unblinded.

256. The initial June 2019 and BLA data sets tracked the same metrics for the same visits for the same patients. No additional data were collected in connection with the BLA data set. Yet as revealed in the Final Massie Report, there were discrepancies between the June 2019 data set and BLA data set.

257. In the June 2019 data set, the p-value for the first secondary endpoint in Study 302 was 0.0620.[20] The Statistical Analysis Plan required that Biogen halt evaluation of endpoints once it reached a statistically insignificant endpoint. Thus, because the first secondary endpoint was not positive, Biogen's argument that the secondary endpoints supported approval was invalid.

258. In the BLA data set, the p-value for the first secondary endpoint in Study 302 changed to 0.0493. The subtle change of a few patient records while Biogen was purportedly "cleaning up" results had a suspiciously outsize result on the outcome of the aducanumab clinical trials. Though challenged on this point by Dr. Massie, neither Defendants nor the FDA have explained the discrepancy.

VII. LOSS CAUSATION

A. The FDA empanels an advisory committee

259. "When a scientific, technical, or policy question arises, such as whether an unapproved product is safe and effective, FDA often relies on Advisory Committees to provide

[20] A p-value of 0.05 or less is statistically significant under the statistical analysis plans.

independent advice." "Committees typically are asked to comment on whether adequate data support approval, clearance, or licensing of a medical product for marketing." "The primary role of an advisory committee is to provide independent advice that will contribute to the quality of the agency's regulatory decision-making and lend credibility to the product review process." "***Advisory committee meetings often receive considerable media attention, and the agency welcomes such scrutiny because it helps provide public assurance of a responsible process***." [21]

260. It was inevitable that aducanumab would face an advisory committee because the FDA's process badly needed credibility:

a. The potential consequences were immense. If aducanumab were approved, it would be prescribed to hundreds of thousands, perhaps millions, of patients. It would become the only disease modifying therapy for Alzheimer's Disease. It would cost tens of billions of dollars each year and overwhelm the country's PET and MRI scan capacity.

b. The data are controversial. Aducanumab had two Phase III trials. One partially succeeded; the other failed. In any other case, the FDA would have instructed the sponsor to conduct another Phase III trial, but here, the FDA sought to approve aducanumab without any further trials.

c. The history is controversial. Biogen declared futility as to the aducanumab trial. It then declared that it erred in declaring futility.

d. There is significant pushback from physicians. A large number of physicians believe aducanumab should not be approved.

[21] U.S. Food & Drug Administration, Advisory Committees: Critical to the FDA's Product Review Process, available at https://www.fda.gov/drugs/information-consumers-and-patients-drugs/advisory-committees-critical-fdas-product-review-process

261. Thus, as stock analysts recognized, the decision of the advisory committee would be a critical factor in the success of aducanumab.

a. In an October 24, 2019 report, an SVB Leerink analyst wrote that "FDA Approval is Likely though Scrutiny from Advisory Committee Seems Inevitable."

b. In a November 20, 2019 report, Cowen analysts wrote that "[a]n advisory committee review for aducanumab is a near certainty. [] It is far more likely that the agency will want to convene a panel review to discuss the unusual efficacy analyses and explain its thinking (positive or negative) before acting."

B. The FDA Releases Effusive Briefing Materials and Buries the Massie Report

262. On November 4, during trading hours, the FDA released briefing materials ("Briefing Materials") for the Aducanumab Advisory Committee meeting.

263. The Briefing Materials included:

a. A report from the FDA and Biogen which, together with Appendices 1 and 2 thereto, ran to 343 pages;

b. More than 90 minutes of pre-recorded presentations by Biogen;

c. A 50-minute pre-recorded presentation by the FDA's efficacy reviewer;

d. A 7-minute pre-recorded presentation by the FDA's safety reviewer; and

e. A 45-minute pre-recorded presentation by Massie.

264. On the whole, the Briefing Materials were effusive.

265. For the first time in FDA history, the FDA and a sponsor filed joint briefing materials. Their joint report set out Biogen's position; the FDA inserted short, paragraph-long comments, the majority of which simply said the FDA agreed with Biogen's position.

266. The FDA characterized EMERGE as "highly persuasive" evidence of aducanumab's efficacy.

267. The FDA found that EMERGE was a positive study and set about trying to find reasons why ENGAGE was wrong rather than evidence that aducanumab was ineffective:

> A guiding principle of the hypothesis was that if aducanumab is effective and the effect is dose-related as in Study 302, it follows that patients in Study 301 with adequate and consistent dosing should also demonstrate an effect on clinical endpoints.

268. The FDA agreed that Biogen could use a Phase Ib study, Study 103, as a supporting study to approve aducanumab, even though it was an exploratory study.

269. The FDA concluded that "[t]he effect of aducanumab in Study 302 is ***robust and exceptionally persuasive*** on ***several*** of the instruments used to evaluate efficacy."

270. Appendix 1 to the 343-page report was a clinical review report by Dr. Kevin Krudys. Dr. Krudys, who had recently moved to the Office of Neurology, reports to Dunn.

271. The Clinical Review Report concluded that "the applicant has provided substantial evidence of effectiveness to support approval."

272. The Advisory Committee was asked to vote on and discuss certain questions. As Advisory Committee Members themselves would note, the questions were heavily biased in favor of approval. The first voting question required the Advisory Committee to simply ignore ENGAGE. The second asked the Advisory Committee to state whether the Phase Ib study provided support. The third asked the Advisory Committee to state whether Biogen had shown evidence that aducanumab removed amyloid plaque – regardless of whether the removal did anything to reduce cognitive decline in Alzheimer's patients. The fourth asked whether Study 103 and Study 302 supported approval in light of the post hoc analysis of Study 301. Analysts noted that these were leading questions designed to support approval:

a. In a November 4, 2020 report, a J.P. Morgan analyst wrote that "[w]e see the FDA position as highly supportive of approval and believe the questions presented to the panel are structured to reinforce the FDA position."

b. In a November 5, 2020 report, an RBC analyst wrote that the "[d]raft questions [are] clearly designed to steer AdComm panelists favorably."

273. Appendix 2 to the Joint Report, beginning on page 247 of the Briefing Materials, was the Draft Massie Report.[22] Unlike the other reports, the Draft Massie Report bore a prominent DRAFT watermark. To Plaintiffs' knowledge, no statistical review presented to an FDA advisory committee has ever been identified as a draft. Thus, the FDA's highly positive clinical review and presentation and other indicia suggested that the FDA would give the Draft Massie Report short shrift. This is what a UBS analyst concluded in a November 5, 2020 report which stated that the Draft Massie Report was "buried at the end of the documents and seemed superseded by FDA's prior commentary."

274. Even investors who consulted the Draft Massie Report would not know what to make of it. The Draft Massie Report was written for the world-renowned experts who sat on the Advisory Committee, not investors. It was dense to the point of being impenetrable. It contained almost one hundred pages of statistical analyses. The analyses were organized by Study rather than topic, so finding the same analysis of Studies 301 and 302 requires sifting through dozens of pages. Some of the Draft Massie Report's analyses were based on information that had already been made public, which could give the impression that it contained nothing new.

[22] The Draft Massie Report is attached as Exhibit 3 hereto and is incorporated by reference.

275. It was nearly impossible in the short time provided before the close of trading on November 5 for investors to appreciate the Draft Massie Report on its merits. Investors would have to pore over the Massie Report to discover that it revealed shocking new data to which Biogen and the other portions of the FDA had no answer. As further set out above, the Massie Report revealed that: (a) the effects on Non-Carriers was essentially nil; (b) PV4 had no impact on Carriers in Study 302; (c) in both Studies 301 and 302, Carriers whose titration was interrupted by ARIA experienced better clinical outcomes than Carriers whose titration was not interrupted and so received more 10mg/kg doses; (d) the number of 10mg/kg doses had no impact on Carriers in Study 302; (e) there was no correlation between the amount of amyloid plaque removed and clinical outcomes; (f) there was wide variation in treatment effect between countries and the U.S. performed poorly; (g) younger patients and those whose Alzheimer's disease was less advanced achieved worse outcomes; and (h) the multiple endpoints were closely correlated. The Draft Massie Report leveled devastating, unanswerable criticisms against the case Biogen made for aducanumab's approval.

276. Analysts focused on the laudatory position the FDA took in the Briefing Materials. Further, several analysts did not mention the Massie Report at all. Thus, it is plain that even analysts whose job was to cover Biogen had not read the Draft Massie Report but had noticed the FDA's clear bias in favor of approval:

a. In a November 4 article which did not mention the Draft Massie Report, a Cantor Fitzgerald analyst reported that "[s]imply put if you look at the documents and see how many times in the FDA position box that they say 'we agree' it suggests that Biogen's key arguments are now well positioned into Friday's AdCom";

b. On November 4, a Guggenheim analyst published a report titled *Adu Briefing Docs Are Out, Draft Questions Sets Up For A Positive Vote; Approval More Likely Than Not*; it did not mention the Draft Massie Report;

c. On November 4, an H.C. Wainwright analyst published a report which did not mention the Draft Massie Report and stated that "[b]riefing documents augur well for Friday's AdCom[.]";

d. On November 4, a Jefferies analyst published a report which did not mention the Draft Massie Report titled *Hot Debate but FDA Clearly Reads Positive on Efficacy, Safety*, which provided that "FDA tea-leaves read much more positive than consensus.";

e. On November 4, an RBC analyst published a report titled *FDA Drinks the Adu Kool-Aid, Showing Surprising Openness to Approval Despite Mixed Data; Friday's AdCom Still Key*, which provided "we believe the briefing documents read more amenably than even Street bulls would have expected."; and

f. On November 4, a Barclays analyst published an article titled *Adu Briefing Documents Highlight Supportive FDA Stance*, which provided "outside of the statistical review team portion (which was buried deep in the Briefing Documents, raised much of the same issues brought up by the Street, and whose conclusions were largely ignored otherwise), this represents the near-best case scenario for [Biogen] shares."

g. A February 5, 2021 article quoted Marc Goodman, an SVB Leerink analyst, as saying:

> There was a special relationship. You could crystal-clearly see it. The briefing documents were unprecedented. I've been doing this job over 20 years and I've talked to people who have been doing it longer, and we've never really seen anything like that before, where the FDA is just working that closely with a company. They went to the [advisory committee] basically saying, "This drug's getting approved."

277. Other analysts published initial reports that noted the laudatory language and ignored or downplayed the Draft Massie Report, but published later reports that reported showing the data it revealed were devastating.

a. In a mid-day November 4 report, a J.P. Morgan analyst published a report titled *To Be Brief … the FDA Wants to Approve Adu*. The report mentioned the Draft Massie Report's bottom-line conclusion in passing. In a second report issued that evening after close of trading titled *A Closer Look at the Adu Briefing Docs and The Tale of Two FDAs* noted that "[o]ur more thorough review was eye opening in terms of conflict of opinions between the FDA reviewers and their statisticians, who are far more negative." The second report sarcastically noted in response to one of the FDA's more egregious analyses "Data mine much?" The J.P. Morgan analyst then wrote that it was "surprising" that Non-Carriers did not achieve any benefit and that it "conflicts with [Biogen]'s hypothesis that high aducanumab dosing leads to a better benefit as non-carriers were always able to dose up to 10mg/kg." Thus, though the analyst's initial review was favorable for aducanumab and its approval, the analyst's more thorough review showed that the data presented in the Draft Massie Report undermined the case for approval;

b. On November 4, a Raymond James analyst published a report titled *Briefing Documents: "Do Stats Matter?"*, which provided that "[t]he briefing documents for aducanumab are a landslide win for [Biogen] and increase the likelihood of aducanumab approval substantially." The Raymond James analyst noted that there was a Draft Massie Report which disagreed, but noted that "[i]t's going to take us most of the day to go through it all[.]" On November 5, the same analyst published a second report which provided:

> The effusive briefing documents indicate adu *may* be approved[] [h]owever, we were not persuaded by any new data/analysis that aducanumab actually works. In fact, our conviction that the drug probably doesn't work is increased. Put differently, we completely agree with the statistician who essentially annihilated the pro-aducanumab

> position put forth by the clinical efficacy reviewer ("***unscientific, statistically inappropriate, and misleading***").
>
> * * * * *
>
> ***Weak correlation between plaque reduction and CDR-SB. The correlation between plaque reduction [] and the primary endpoint [] has an R^2 value of just 0.13 [sic], which calls into question the amyloid hypothesis entirely if it wasn't questioned enough already.***

c. On November 4, 2020, a UBS analyst published an article titled *First pass of briefing docs suggest FDA has constructive view – this changes everything*. On November 5, the same analyst published a second report providing:

> ***Clinical Review vs. statistical review – clinical clearly prevails here***
>
> The experts [consulted by the analyst] noted the stark dichotomy in opinion between the clinical review (favoring approval) and the statistical review (against approval, recommending additional trial. The experts noted that prior to publishing the briefing doc, sign-off at the director office level is required[23] and so the overall conclusion of the docs (stating [Biogen]'s trial results provide evidence of efficacy and support approval) essentially implies the FDA is willing to overcome the statistical shortcoming in light of the positive clinical review.

d. The Director in Chemical Biology & Research in the Novartis Institute for Biomedical Research published an article which provided that:[24]

> The fact that Biogen stock jumped on the release of this document tells you most of what you need to know about the stock market (and about investing in biotech stocks in particular). You wonder how many people even got as far as the statistical review section before hitting the big green Buy button.

278. Because the FDA made it clear it wanted to approve aducanumab and investors did not have enough time to consult the Draft Massie Report, or understand its findings, Biogen's stock price increased to close at $355.63 on November 4, 2020.

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[23] While director sign-off is sometimes required as a matter of office policy, in practice, the directors typically delegate the decision to the heads of offices – here, Billy Dunn, who favors approval.

[24] The report was published on November 9, 2020, but was written before the Advisory Committee meeting.

279. Yet on November 5, some investors began to digest and give credence to the information that had been made public, though buried, in the Draft Massie Report. On November 5, Biogen's stock fell to close at $328.90, down 7.5%.

C. The Advisory Committee Votes 10-0 Against Approval

280. The Advisory Committee meeting was scheduled to begin early morning Friday November 6 and continue until after trading closed. That day, trading in Biogen's shares was halted and would only resume on Monday November 9.

281. Late Friday, the Advisory Committee discussed and voted on the FDA's questions. The panel's votes were:

> Question 2: Does Study 302, viewed independently and without regard for Study 301, provide strong evidence that supports the effectiveness of aducanumab for the treatment of Alzheimer's Disease?
>
> Yes: 1 Uncertain: 2 ***No: 8***
>
> Question 4: Does Study 103 provide supportive evidence of the effectiveness of aducanumab for the treatment of Alzheimer's Disease?
>
> Yes: 0 Uncertain: 4 ***No: 7***
>
> Question 6: Has the Applicant presented strong evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology [i.e., does aducanumab reduce amyloid plaque]?
>
> Yes: 5 Uncertain: 6 No: 0
>
> Question 8: In light of the understanding provided by the exploratory analyses of Study 301 and Study 302, along with the results of Study 103 and evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology, is it reasonable to

consider Study 302 as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease?

Yes: 0 Uncertain: 1 ***No: 10***

282. The cause of the panel's dissatisfaction was the facts revealed in the Draft Massie Report.

283. A panelist, Dr. Caleb Alexander, objected to treating EMERGE as a positive study, because:

> I think even with study 302 there are some reasons for question. One is that there's no correlation between plaque reduction and week 78 outcomes.[]
>
> Then the last that I'd say is that, once again as pointed out by the FDA's own [statistical] reviewer, there's no consistent effect across [APOE4] subgroups in 302, yet one would hope to see this with a strong efficacy signal.

284. Dr. Aaron Kesselheim, another panelist, raised the same objection:

> I would have loved to see also a mediator analysis on whether the changes in plaque explain much of the differences in the cognitive endpoints, which is of course the burden of proof. The burden of proof is we targeted the oligomers of the amyloid hoping that that would have an impact clinically, and our question is does that bear up; if it's a strong enough effect? I must say I care more about the clinical aspects [i.e., clinical outcomes] than I do about the pathology.

285. As did a third, Dr. Joel Perlmutter:

> I think we see a lack of correlation between the A-beta change and the clinical endpoint CDR-SB. I think that's a concern.

286. A fourth, Dr. Madhav Thambisetty:

> I would point to slide 20 of the FDA statistical reviewer's presentation, where you examine the relationship between change in global brain amyloid burden at week 78 in individuals exposed to high-dose aducanumab and change in the CDR sum of box scores. There really appears to be no relationship either in Study 302 or 301, and this appears to be the case even when the analysis is restricted to only individuals exposed to the 10mg/kg dose.
>
> I think there are some larger implications of these findings which we are not tasked with discussing today. One of the larger questions relevant to these observations is whether

> lowering brain amyloid burden is in fact the correct target in Alzheimer's disease, but like I said, I think that's beyond the remit of the discussion today.

287. Perlmutter, an expert on PET imaging, stated that "the disconnect or the lack of correlation with the clinical benefit is a real problem."

288. Asked whether Study 103 supported approval, Alexander pointed out that the fact that "contrary to 302, the effect was larger in non-carriers than carriers" "gave [him] pause."

289. Summing up, Dr. John Duda, a panelist, stated:

> But I think, all in all, the main -- I think several of us have said it already. Dr. Massie's criticisms just were never addressed in the clinical overview, and there seemed to be a disconnect between different aspects of the FDA reporting that are very difficult for us to draw conclusions from. So in light of that, I think it makes it much more difficult to get where the FDA maybe thought we would go today.

290. Dr. Scott Emerson:

> I'm highly critical of the fact that the FDA presentation today was so heavily weighted to just giving the same conclusions that the sponsor did, and that there was no[] presentation by the statistician who'd done a careful analysis and made many points that I was very glad to see that the committee read.

291. Kesselheim:

> I also wanted to echo what others have said, to thank the FDA, and the sponsor, and Dr. Massie in particular, for their thorough reviews of the material and very helpful presentations.

292. Thambisetty:

> I voted no as well for all of the reasons discussed throughout the day, and I'd also like to take the opportunity to thank both the applicant and the FDA for the privilege of reviewing this hugely important work. I'd also add a special note of thanks to Dr. Tristan Massie for a really thorough statistical analysis that was very, very useful.

293. The closely-watched advisory committee publicized, and showed the significance of, the data set out in the Draft Massie Report. Further, the Advisory Committee was made up of world-renowned experts. Their decision showed to investors that Massie's analyses were reliable.

294. On November 9, Biogen's stock resumed trading opening at $230.82 per share, and closed at $236.26 per share, down 28.2%.

295. Dunn's office compromised its statistical rigor to push approval of an Alzheimer's Disease treatment. The November 6, 2020 Advisory Committee Members said as much. At that meeting, Advisory Committee Member Dr. Scott Emerson would accuse the FDA of "complicity" with Biogen in putting forth unacceptable statistical analyses and add that he was "very, very, very disturbed by some of the analyses that were considered" by the FDA. Dr. Caleb Alexander, another, would observe that the FDA does "an extraordinary amount of explaining around the contrary findings". Alexander would also add that "***I have a very hard time understanding***, after carefully reviewing what I thought was a very well done and well-articulated [FDA] biostatistical review, which convincingly argued the evidence was 'at best compellingly conflicted,' ***how the FDA could conclude that there are substantial evidence of effectiveness****[.]"* Nearly all Advisory Committee members would complain that the FDA "foisted" "biased" leading questions on them designed to support approval of aducanumab.

296. Stock analysts whose job is to evaluate and comment on Biogen as an investment were also struck by the FDA's loose standards:

a. Baird: In a November 2020 note quoted in a November 7, 2020 Biopharma Dive article, Baird analyst Brian Skorney wrote that "[i]t is abundantly clear that whatever relationship FDA [Office] Director Dr. Billy Dunn has with aducanumab, his objectivity is completely lost."

b. BMO: In a November 9, 2020 report, a BMO analyst wrote "Rather than seeking ad-com advice as would be customary, it seemed to us that FDA was instead seeking validation for its unorthodox interpretation of a-mab clinical data. However, the committee would have none of it. Because the two Phase III studies [] were identical and impeccably conducted at the same

time, it would be negligent to regard EMERGE as a stand-alone trial while using only favorable retrospectively-derived elements from ENGAGE to support the EMERGE outcome."

c. J.P. Morgan: After the Advisory Committee vote, a J.P. Morgan analyst wrote in a November 8, 2020 report that "we don't at all understand why [the FDA] were so pro-adu in the first place".

d. Morgan Stanley: In a November 6, 2020 report, a Morgan Stanley analyst wrote that "[w]e are frankly perplexed why the FDA held the advisory committee, given it knew its position would be controversial."

e. Piper Sandler: In a November 8, 2020 report, an analyst employed by Piper Sandler wrote that "with Billy Dunn [] running point, FDA went to great lengths – including in the structure and positioning of the questions – to set the stage for a positive review[]" adding that "it's our opinion that a CRL [a rejection] is the right thing to do."

f. Wedbush: A Wedbush analyst wrote in a November 8, 2020 article wearily titled *We Repeat, Does the Aducanumab AdCom Really Matter? [Hint: No, Don't Think So]*:

> [] Ultimately, the AdCom voted 10-0 (uncertain = 1) the EMERGE ("302") study does not serve as primary evidence of effectiveness of aducanumab in Alzheimer's disease (AD). Since this was the only "successful" study, approval would seem to be at risk. Panelists rightfully objected (in our view) to a range of statistical and clinical trial analyses/conclusions. However, we still pose the question: does this vote even matter? In our view, FDA intertwined itself with [Biogen] and appears set to approve the drug regardless. In a year where we've seen other not-ready-for-prime-time approvals (e.g. hydroxychloroquine), we would not be surprised if the agency diverges from the AdCom's recommendations and approves aducanumab.

297. In December 2020, good government advocacy group Public Citizen published an open letter calling for an investigation of the FDA's collaboration with Biogen concerning aducanumab, which observed:

> It seems likely that, but for the statistical review provided by Dr. Massie and the intervention of the FDA's [] Advisory Committee — whose members had not been subject

> to the apparent regulatory capture that compromised the independence and objectivity of the senior staff and clinical reviewers in CDER's Office of Neuroscience — the FDA was prepared to rush to the U.S. market a drug for Alzheimer's disease that lacks substantial evidence of effectiveness, despite these potentially catastrophic impacts.

298. In a November 9, 2020 note, the Director in Chemical Biology & Research in the Novartis Institute for Biomedical Research explained Biogen's rationale in pursuing aducanumab approval:

> [Biogen] have enough of a hint to run a better confirmatory trial, should they so desire, but they do not. They desire to go to the FDA, get the drug approved, and begin printing money.
>
> And I would be all for a drug company printing money if they had a drug that could really alter the course of Alzheimer's disease, but (once again) Biogen has not, in my opinion, demonstrated that they have anything like that. And I am definitely not all for a drug company printing money for something that really doesn't do anyone any good. Because everyone knows what's going to happen if aducanumab is approved: the pent-up demand for something, anything to treat Alzheimer's is immense. Has been immense forever. There are a lot of people who have a family member with the disease, and they will demand treatment with the new drug that the FDA has approved to fight the disease. Who could blame them?
>
> * * * * *
>
> And if [the FDA approves aducanumab], we'll find out how many physicians will prescribe it, and how many insurance companies will pay for it. It would be something to see both of these groups hold the line, but I fear that the pressures will be just too great. Biogen is counting on just that, and I'm not happy about it.

299. Extraordinarily, after publication of Massie's report showed Defendants' statements were false, even investment analysts who covered Biogen opined that approving aducanumab on the basis of the data Biogen presented is not only unlikely, but scientifically and morally wrong:

a. In a November 6, 2020 report, an analyst employed by Raymond James noted:

> Honestly, the panel was a disaster for aducanumab. And it is completely justified. There is no serious scientific argument in favor of anything other than a new prospective study of aducanumab and we can't explain FDA's effusive stance on aducanumab 1) pre-submission, 2) in the briefing documents, and who knows maybe 3) going forward, if they ultimately approve aducanumab.

> If [aducanumab] is approved, 1) futility analyses don't matter, 2) statistics don't matter, 3) AdCom panel votes don't matter, 4) FDA's own guidance/statutes don't matter, and we're left wondering what actually matters in determining what drugs make it to market.[] One coherent bull case may be: FDA's credibility is seriously in question already given the irreconcilable interface of the briefing documents and the panel's views, so there is limited credibility left to destroy by approving aducanumab.
> **Lastly, FDA should COUNT THE VOTE!**

b. In a November 9, 2020 report, a BMO analyst castigated the FDA on grounds that "[r]ather than seeking ad-com advice as would be customary, it seemed to us that FDA was instead seeking validation for its unorthodox interpretation of a[ducanu]mab clinical data." The analyst called on Biogen to withdraw its BLA outright on moral and scientific grounds, ***regardless of whether it still might be approved***, and start a new Phase III trial.

VIII. THE FDA APPROVES ADUCANUMAB BASED ON AN UNVALIDATED ENDPOINT

A. The FDA Tells Biogen At the June 2019 Meeting that FDA Might Be Willing To Approve Aducanumab Based On Surrogate Endpoints

300. At the June 2019 Meeting, the FDA told aducanumab may be approved through a pathway that had never been used before for Alzheimer's drugs: accelerated approval. Accelerated approval does not mean the FDA approves a drug more quickly. Rather, it means the FDA approves a drug even though the sponsor has not shown that it is effective. To be eligible for accelerated approval, the applicant must show, among other things, that the clinical trials have an impact on a surrogate endpoint, which is a marker that is used as a substitute for a direct clinical measure. To be used, surrogate endpoints must be validated, meaning that there must be "extensive evidence [] including evidence from epidemiological studies and clinical trials" showing that the endpoint is "reasonably likely to predict clinical benefit".

301. The FDA's openness was surprising. The FDA had declared as late as 2018 that there were no surrogate endpoints for Alzheimer's Disease. In its 2018 Guidance for Industry titled *Early Alzheimer's Disease: Developing Drugs for Treatment*, the FDA stated:

> Although the issues and approaches discussed above for Stage 2 patients [those who have begun to see subtle impairments] are relevant for Stage 1 [asymptomatic] patients, there is unfortunately at present no sufficiently reliable evidence that any observed treatment effect on such biomarker measures would be reasonably likely to predict clinical benefit (the standard for accelerated approval), despite a great deal of research interest in understanding the role of biomarkers in [Alzheimer's disease].

302. Nothing had happened since and the FDA has never announced anything that would provide grounds to change the FDA's mind.

303. Further, the minutes of the December 2014 Meeting show that the FDA had told Biogen there was no current appropriate biomarker, nor would there be absent "expert consensus":

> Given the lack of a scientific consensus as to which biomarker outcome measure (or set of measures) might be most appropriate for helping confirm that a compound is [redacted] in Alzheimer's disease, the inclusion of the analysis of a specific biomarker-derived measure [] is premature. Instead, [a pre-specified detailed statistical analysis plan] will allow for the possibility that if an expert consensus is later reached that a specific biomarker-derived outcome measure [] is the most appropriate for supporting a claim that a compound is [redacted] in Alzheimer's Disease, a pre-specified detailed plan will already exist for its analysis.

304. Yet the June 2019 Meeting's minutes provided: "A further possibility that the sponsor may give consideration to, depending on what further analyses demonstrate, is to seek accelerated approval of Aduhelm based on its effect on reducing brain amyloid." The minutes continued: "[s]uch an approval would be predicated on the conclusion that an effect of Aduhelm in reducing brain amyloid would be reasonably likely to predict clinical benefit." But the FDA made clear in the minutes, the results would have to show a correlation between clinical outcomes and amyloid reduction: "***Presumably, such a conclusion would be supported by the clinical efficacy data that exists in the patients that experience reductions in brain amyloid.***" As alleged

above, the Study 301 and 302 data showed that clinical outcomes and brain amyloid were ***not*** correlated.[25]

B. The FDA and Biogen Assure the Advisory Committee They Are Not Considering Accelerated Approval Based On A Surrogate Endpoint Thereby Preventing the Committee From Advising That Such Approval Would Not Be Warranted

305. At the Advisory Committee meeting, the FDA represented that the FDA would not approve aducanumab on the basis of a surrogate endpoint:

> Perlmutter: [The question is] for the sponsor. It could be answered by either one, actually, two related questions.
>
> One is, in 301, if the high-dose response – the lack of response was due to a lower dose, but yet the lower dose in 301 provided [a] benefit, was the lower dose in a high dose lower than the lower dose? Does that fit on the dose-response curve?
>
> Then the second part of my question is if we're using the PET A-beta measurements as a biomarker of efficacy, wasn't there a lack of correlation between the response in the PET findings with the CDR-SB, and how do you explain that if that biomarker is relevant for their clinical benefit?
>
> Dunn: This is Dr. Dunn. I can speak to the second one. ***We're not using the amyloid as a surrogate for efficacy.***
>
> * * * * *
>
> Fountain: I think we have the opportunity now to ask the FDA a question about the correlation of amyloid with clinical change in Study 302. I'm not sure who's Dr. Dunn, Dr. Krudys, or someone else is going to address that.
>
> Krudys: [] And second, I'll just say that ***it's not like change in beta-amyloid are being used as a surrogate here.*** It's a biomarker of what the drug is doing, and there is some correlation between the changes and changes of clinical outcomes.

306. As set out above, the FDA's Question 6 asked the Advisory Committee to vote on whether aducanumab reduced amyloid plaque. After the Advisory Committee voiced objections that biomarker data was not correlated with clinical outcomes, Dunn interjected to accuse the

[25] The STAT journalists claimed in their article claimed that a person had read the minutes to them. The minutes were later published, and confirmed that the STAT article's quote was accurate, word for word.

panel of intentionally preventing him from clarifying that the FDA was not interested in the panel's views about the correlation between biomarkers and clinical outcomes:

> Thambisetty: If I think that there's good biomarker evidence for brain pathology but not good biomarker evidence for clinical efficacy, how would I vote on this question?
>
> Fountain: You'll have to decide for yourself if that constitutes strong evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology.
>
> Thambisetty: Got you. So you think the term "pathophysiology" would also include treatment effects and therapeutic efficacy?
>
> Dunn: Dr. Fountain, you may intentionally be not wanting me to clarify –
>
> Fountain: No –
>
> Dunn: -- in order to –
>
> Fountain: -- that would be great if you'd clarify.
>
> Dunn: Okay. It's always interesting to work on questions hard and then see how people read them. This question was absolutely intended to represent the biomarker-based assessment of the pathology of Alzheimer's. Really, we're talking about amyloid and tau, and there was also obviously some downstream effects, not specifically. But that's what we're talking about here, mainly amyloid. ***But it's not a clinical meaningful question. It's about what effect has been demonstrated using the biomarkers that we have on the pathophysiological findings.***

307. Expressly relying on the FDA's assurances, Advisory Committee voted "yes" or "uncertain" to the question posed, rather than "no":

> Kesselheim: I voted uncertain because while it is very clear that the drug provides substantial impact on the biomarkers that it measured, ***because the effect of the changes in those biomarkers on the clinical impact of the drug is unclear, that left me uncertain as to whether or not it had an impact on Alzheimer's disease pathophysiology.*** Thank you.
>
> * * * * *
>
> Onyike: Yes. This is Chiadi Onyike. I voted yes. I viewed the question narrowly. ***This is a treatment designed to basically [indiscernible] out amyloid pathology, so I view the question as did it actually do that***. There's clear evidence that it did that in a dose-related fashion.
>
> * * * * *

Duda: This is John Duda. I voted yes because I do believe ***there's strong evidence of a pharmacodynamic effect on Alzheimer disease pathology, specifically amyloid pathology, and in my mind that justified a yes.*** Thanks.

* * * * *

Dr. Richard Hoffman: Yes. I voted yes, but ***primarily because it was mentioned that we were just talking about amyloid beta and tau.*** But again I'd like to point out that I think there are a number of other proteins that are misfolded that could be involved in Alzheimer's that we really don't understand yet. I think that's the reason why you didn't see super excellent results with this drug because if it was targeting all the toxic species, I think we would have seen much better efficacy results. Thank you.

* * * * *

Dawndra Jones, DNP, RN, NEA-BC: Yes. This is Dawndra Jones. I voted yes because I believed ***it clearly demonstrated positive impact on the biomarkers, especially concerning the amyloid pathology***. Thank you.

* * * * *

Perlmutter: Well, I said uncertain, and I agree with everybody actually. ***I think there's no question it demonstrates engagement with the A-beta amyloid. I think the tau is very uncertain. The question in my mind is whether that's the correct biomarker to use for the relevant clinical effect.***

* * * * *

Alexander: I voted uncertain. [] Regarding this question at hand, I think it is, as was noted, important to note that the absence of correlation between the reduction in amyloid and clinical efficacy, at least among the high-dose group, ***I do think there's very good evidence that the product reduces amyloid. But as was noted, the impact on tau was more difficult to understand the meaning of that because it was among what I understand to be a selected or non-random subset.*** Thank you.

* * * * *

Emerson: I tended to answer this narrowly as did Dr. Onyike. ***The pathophysiology of Alzheimer's include signs of amyloid deposits. I think this has affected that. Whether it has affected symptoms or clinical sequelae that matter more is unclear, but in the sense that something has changed, I said yes.***

C. The FDA Grants Accelerated Approval of Aducanumab Based On A Surrogate Endpoint

308. Biogen could not have found a better partner than Dr. Billy Dunn. Dr. Jarrow, who worked closely with Dunn, describes him as "stubborn": "I've had a lot of experience within

Medical Policy and Program Review Council meetings, and [Dunn] gets to a conclusion, and then after you bat down the reasons to support his conclusion, he just finds new ones."[26]

309. That's exactly what happened. According to a July 20, 2021 *New York Times* article, on March 31 and April 7, 2021, the FDA's influential Medical Policy and Program Review Council met to discuss aducanumab.

310. The Medical Policy and Program Review Council is an internal FDA group that meets weekly to discuss pressing policy and regulatory issues. Its members include some of the most senior employees of the Center for Drug Evaluation & Research and the Center for Biologics Evaluation & Research. It is staffed with a variety of the FDA's most renowned experts. Its function is to advise on policy and program issues, including novel, challenging and potentially unresolved medical issues.

311. The July 20, 2021 *New York Times* article recounts that the "vast majority" of the Medical Policy and Program Review Council's 15 members voted against approving aducanumab. According to the meetings' minutes, one member said approval could "result in millions of patients taking aducanumab without any indication of actually receiving any benefit, or worse, cause harm."

312. With no good answers to the correct criticisms leveled by Massie, the Advisory Committee, on June 7, 2021, Dunn and his colleagues sidestepped them.

313. According to the *New York Times*, the head of the FDA's Office of Oncology, Dr. Rick Pazdur, briefly raised the idea of accelerated approval. Cancer is lethal and develops quickly, and many cancers are rare so that patients are difficult to recruit for clinical trials, while there is

[26] UBS analyst report dated December 4, 2020.

general agreement in the literature that certain markers like progression-free survival accurately predict overall survival. Thus, accelerated approval is used frequently in oncology.

314. Dr. Patrizia Cavazzoni, the head of the FDA's Center for Drug Evaluation and Research, convened an April 26 meeting to determine whether to approve aducanumab. Cavazzoni invited Pazdur and the head of the FDA's vaccine program, Dr. Peter Marks, to the meeting, even though neither office has anything to do with Alzheimer's disease.[27] She allowed them to vote on whether aducanumab should be approved.

315. A majority of the attendees voted to approve aducunamab using the accelerated approval pathway because it reduced amyloid plaque.

316. The FDA approved aducanumab ***despite*** the fact that its clinical trials did not show efficacy, not because they did:

a. The approval was supported by a concurring memorandum from Dr. Peter Stein, the director of the FDA's Office of New Drugs. Stein concluded in his memorandum that "***the evidence is not sufficiently compelling or persuasive to meet the substantial evidence standard for standard approval***." Stein added that "[t]he statistical review by Dr. Massie provides a detailed assessment of all three studies, raising numerous concerns, only some of which are noted above. I refer the reader to this review."

b. On July 13, 2021 the *Journal of the American Medical Association* published an opinion article written by Dunn, Stein, and Cavazzoni, who wrote the primary approval memorandum. The article was titled *Approval of Aducanumab for Alzheimer Disease – the FDA's Perspective*, showing that the article recounted the FDA's perspective rather than that of the

[27] A summary memo prepared and published by the FDA confirms that Pazdur and Marks attended the April 26, 2021 meeting and voted in favor of approval.

individual authors. In the article, the authors, on behalf of the FDA, made clear that "***residual uncertainty remains about aducanumab's clinical benefit*** [so] as a component of accelerated approval Biogen Inc is required to conduct a postapproval trial to verify benefit."

317. Observers immediately grasped that the FDA decision approving aducanumab was not an application of existing FDA standards but instead a dramatic loosening of these standards:

a. Biogen's stock price immediately shot up, but so did the stock prices of competitors who were developing their own Alzheimer's therapies, including Eli Lilly and Prothena;

b. Eli Lilly had previously contemplated Phase III trials for its own Alzheimer's drug, donanemab, but within weeks of the aducanumab decision, it announced that it would forgo the trials and seek accelerated approval within the year;

c. *Endpoint News*, a biotech industry publication, polled 1,400 industry professionals, and reported on June 9 that 80% disagreed with the FDA's decision to approve aducanumab. One commenter noted that "Aducanumab priced at $56k with the efficacy of a sugar pill is taking advantage of patients, the healthcare system and is ruthless";

d. The American Neurological Association's executive committee notified its members that "**based on the clinical evidence, ADUHELM should not have been approved at this time.**"[28]

e. Dr. Vissia Viglietta, a former Biogen senior medical director who helped design aducanumab's Phase III trials, was quoted in the July 20, 2021 *New York Times* article as saying

[28] American Neurological Association, *ANA Executive Committee Commentary on the FDA Approval of ADUHELM*, available at https://myana.org/publications/news/ana-executive-committee-commentary-fda-approval-aduhelm (emphasis in original).

that "[t]his approval shouldn't have happened. It defeats everything I believe in scientifically and it lowers the rigor of regulatory bodies."

318. The FDA required Biogen to conduct a confirmatory Phase IV trial to prove that aducanumab is safe and effective. Until the FDA takes action upon the confirmatory trial's results, Biogen will be able to sell aducanumab, at a substantial profit.

319. The FDA obligingly agreed to give Biogen until 2030 to complete the trial, thus giving it seven more years to conduct the confirmatory trial than it had taken to conduct the Phase III trials whose results it was purportedly confirming. Hours after approval, Biogen also announced that it would price aducanumab at $56,000 per patient per year. The combination of price and time on the market ensured Biogen could make tens of billions of dollars selling aducanumab – even if it doesn't work.

320. As Dr. Annette Langer-Gould, a Kaiser Permanente neurologist, pointed out at a July 15, 2021 meeting of the California Technology Assessment Forum, a respected independent organization relied upon by insurance to make coverage and payment decisions, "[w]e're talking about reverse Robin Hood. We're taking little bits of money and transferring it to the company."

D. The Aducanumab Approval Decision Sparks Three Resignations, Two Congressional Investigations, a Call From A Senator To Replace the FDA Head, and Calls From A Former HHS and Current FDA Head For An Investigation

321. The aducanumab approval sparked immediate outrage.

322. Three of the Advisory Committee's nine permanent members resigned because of the FDA's decision to approve aducanumab:

a. Kesselheim resigned, calling the approval "probably the worst drug approval decision in recent U.S. history[.]";

b. Knopman told the Washington Post that he did not "wish to be part of a sham process." In an email to FDA officials, he called Aducanumab approval "foreordained" and a "mockery"; and

c. Emerson resigned, noting that "[t]his was the first time that nobody voted for approval of this drug — nobody — and they went against that.".

323. Public Citizen, an influential good government non-governmental organization founded by Ralph Nader, called for the immediate termination of Cavazzoni, Dunn, and acting FDA Commissioner Janet Woodcock.

324. Senator Manchin called for President Biden to replace acting FDA commissioner Janet Woodcock:

> While the approval of a drug provides hope for the millions of Alzheimer's patients and their families, many scientists have second-guessed the scientific benefit of this approval. The FDA's, and in particular Dr. Woodcock's, decision to go against its advisory committee's decision yet again has resulted in at least three scientists resigning from the committee. In his resignation letter, Dr. Aaron Kesselheim noted that this approval was "probably the worst drug approval decision in recent U.S. history."[citation] This brings into question the current interim leadership of Dr. Woodcock, at a time when strong, trusted leadership at our health agencies is most important. At a minimum, the agency should provide an explanation as to why it chose to go against its advisory committee's recommendations. Having a permanent agency head in charge to answer patients and doctors questions on this approval, as well as assure the general public of the FDA's commitment to public health, is imperative, and Dr. Woodcock is not the right person to lead the FDA.[29]

325. The House Committees on Oversight and Reform and Energy and Commerce both launched investigations ("House Investigations") of the aducanumab approval decision, stating:

[29] Letter from Senator Joe Manchin to President Joseph R. Biden, Jr., dated June 17, 2021, available at https://www.manchin.senate.gov/imo/media/doc/letter_to_white_house_regarding_fda.pdf?cb

> "We have serious concerns about the steep price of Biogen's new Alzheimer's drug Aduhelm and the process that led to its approval despite questions about the drug's clinical benefit.
>
> "We strongly support innovative treatments to help the millions of Americans who suffer from Alzheimer's disease, but Aduhelm's approval and its $56,000 annual price tag will have broader implications for seniors, providers, and taxpayers that warrant close examination.
>
> "Our Committees will be investigating this matter so Congress and the American people can better understand why this drug was approved, how Biogen set its price and what impact this will have on research for future Alzheimer's treatments and federal health care programs."[30]

326. Member of Congress Katie Porter also called for HHS to investigate Biogen's contacts with the FDA in connection with aducanumab:

> It appears very clear that Biogen had an inside route to FDA officials and had undue influence over their decision making and the evidence presented in various settings. While I respect the FDA's scientific expertise, it has become clear through various cases, including Rick Bright's whistleblower suit last year and the recent approval of Aduhelm, that too many pharmaceutical executives, lobbyists, and other stakeholders have long had inappropriate access to officials throughout the Department of Health and Human Services.[31]

327. Concerns intensified after the STAT article's revelations. Hearing of the off-the-books meeting between Dunn and Sandrock, the Hon. Donna Shalala, the longest-serving Secretary of Health and Human Services in history, told a STAT reporter that its Office of Inspector General ***must*** investigate:

> ***When you see a report like [the Stat report], you have to investigate it. You cannot hesitate and you can't do it with your general counsel. You've got to send in the Office of Inspector General. I mean, you shouldn't hesitate for one second.***

[30] House Committee on Oversight & Reform, *Chairs Maloney and Pallone Announce Investigation of Biogen's Alzheimer's Drug Aduhelm*, available at https://oversight.house.gov/news/press-releases/chairs-maloney-and-pallone-announce-investigation-of-biogen-s-alzheimer-s-drug

[31] https://twitter.com/RepKatiePorter/status/1412534817749602314

328. Notably, Shalala did not rule out supporting the termination of Woodcock, Cavazzoni, and Dunn himself over their inappropriate involvement in aducanumab approval if internal "law enforcement" found improper conduct. Asked whether they should be fired, Shalala stated:

You've gotta get the facts first. And your law enforcement in the department is the OIG.

329. The House Investigations likewise intensified after publication of the STAT article. On July 12, 2021, representatives Maloney and Pallone sent Defendant Vounatsos wide-ranging document requests including for "[t]he dates, times, locations, attendees, and any notes or minutes taken of all calls and informal and formal meetings or discussions among FDA officials or personnel and representatives of Biogen related to aducanumab, and all related communications[.]" In an accompanying letter, representatives Maloney and Pallone linked their request to the STAT article's allegations of an improper relationship between Biogen and the FDA and, in particular, Dunn and Sandrock's secret meeting.

330. Indeed, the revelations in the STAT article were so jaw-dropping that the FDA even called for an investigation of itself, as set out in a July 9, 2021 letter from FDA head Janet Woodcock to HHS Acting Inspector General Christi A. Grimm:

> [T]here has been significant attention and controversy surrounding the process for review of Biogen's biologics license application (BLA) for Aduhelm (aducanumab) for the treatment of Alzheimer's disease. This includes an ongoing focus on interactions between Biogen and Food and Drug Administration (FDA) staff during the review process. I write, therefore, to request an independent review and assessment of interactions between representatives of Biogen and the FDA during the process leading to the decision to approve the BLA to determine whether any of those interactions were inconsistent with FDA policies and procedures.

331. On July 11, 2021, six Blue Cross/Blue Shield state-level affiliates declined to cover aducanumab. Blue Cross and Blue Shield of North Carolina stated regarding its decision

not to cover aducanumab, "[c]linical studies failed to demonstrate the effectiveness of Aduhelm [.] while documenting significant risks, like brain swelling and bleeding."

332. On July 15, the Cleveland Clinic and Mt. Sinai Health System, the seventh and eighth largest in the Nation, respectively, announced that they would neither stock aducanumab nor administer aducanumab infusions. Mt. Sinai in particular stated that it would wait for the investigation of interactions between the FDA and Biogen. A Mt. Sinai spokesperson noted that as far as the hospital was concerned, the "integrity of the F.D.A.-Biogen relationship" was in question. Within hours, they were joined by the Providence Health Care System based in Renton, WA, whose system includes 52 hospitals and more than 1,000 outpatient clinics. Because of Medicare Part B's cost-plus repayment structure, these entities are acting against their own financial interests.

333. Also on July 15, 2021, a 15-member panel of experts from the California Technology Assessment Forum unanimously concluded that Biogen had not shown that aducanumab is safe and effective. As Dr. Sarah Kremen, who heads the Center for Alzheimer's and Memory Disorders at Cedars-Sinai Medical Center and was an investigator in one of aducanumab's clinical trials pointed out that, at best, "[t]here may be some small number of people who will benefit, but it's hard to know from the study who that will be[.]"

334. A July 2021 survey by Spherix Global Insights revealed that 80% of neurologists had lost confidence in the FDA in the past year. One respondent added:

> The erosion [of my confidence] is based on the disastrously bad decision to approve aducanumab, which seems like a poorly developed and even possibly corrupt decision. I cannot remember a similar situation in which there was so much dismay and disbelief created by an FDA decision. We do not plan to use aducanumab at this time and we no longer know what to think about and how much to trust any future FDA decisions.

335. In sum, in a June 10, 2021 editorial, Bloomberg editors pointed to aducanumab as the poster boy for the failures of the healthcare system which should prompt "[t]he U.S. [] to take a good hard look at its system for approving and pricing medicines."

336. Dr. David Knopman, a standing Advisory Committee member who was recused from the meeting because he had served as an ENGAGE clinical trial site investigator, submitted a comment urging the Advisory Committee not to recommend approval. Knopman explained that "the evidence shows [if aducanumab is approved] it will offer improvement to none, it will harm some of those exposed, and it will consume enormous resources."

> I am a behavioral neurologist who has cared for patients with Alzheimer's disease (AD) for nearly 40 years. I care deeply for patients and their families. I desperately wish for a genuine therapy that substantially slows or reverses the disease. Yet the evidence that aducanumab is that therapy and has any benefits in persons with AD is terribly weak. An objective view of the data presented publicly by the sponsor Biogen in December 2019 fails on several key points to prove that aducanumab is efficacious.
> []
> Further, the most optimistic efficacy signal from EMERGE for aducanumab provides no support for a claim of improvement while the magnitude of the slowing of clinical progression is exceedingly small. We acknowledge an inability to extrapolate the effects of aducanumab beyond 18 months, but based on 18 month data, the benefit is of questionable clinical benefit.
> []
> These are extraordinary times for so many reasons, but for the Alzheimer world, a decision by the FDA on November 6 would be transformative - in my view more unfavorable than otherwise. Perfection may be the enemy of the good, but for aducanumab, the evidence doesn't even rise to "good." Contrary to the hope that aducanumab will help Alzheimer patients, the evidence shows it will offer improvement to none, it will harm some of those exposed, and it will consume enormous resources.
>
> The straightforward solution is this: Biogen needs to do a third trial with high dose aducanumab. If the drug's benefits are truly substantial, such a trial could recruit quickly and only several hundred patients would need to be randomized.

337. As revealed at the July 15 California Technology Assessment Forum, the Alzheimer's Association estimates that the U.S. will spend about $28 billion per year on

aducanumab, or more than it spends on NASA. Analysts' estimate range between $25 billion and $35 billion per year.

338. To qualify for aducanumab, patients must receive an amyloid PET, a procedure which costs $5,000-$7,000.[32] Moreover, the entire U.S. PET scan capacity is insufficient to aducanumab's needs.[33]

339. Aducanumab is administered through a one-hour infusion every 4 weeks, with no preplanned stopping point. A caregiver must accompany the patient to the infusion.

340. Aducanumab's side effects include ARIA for Carriers, which may cause death. As Biogen admitted in its Advisory Committee presentation, patients will likely need to undergo routine MRIs to screen for a brain hemorrhage. In aducanumab's Phase III clinical trials, each patient received 7 MRI scans during the 78-week treatment. These scans are time-consuming and expensive. Moreover, unless they are interpreted by specialists like those who worked on the aducanumab Phase III trials, the scans may miss cases of ARIA that could kill patients.

341. The clinical benefit of aducanumab, even if it existed, would be miniscule. As it reported on October 27, 2020, analyst firm UBS had asked five Alzheimer's Disease professionals to report the minimum clinically meaningful reduction. Three of five experts said 1 point on the CDR-SB scale; the two others said 0.5 points. According to an August 2019 article published in Alzheimer's & Dementia, a journal published by the Alzheimer's Association, the minimum clinically meaningful improvement is 1 point on the CDR-SB scale. Yet even in EMERGE, the reduction in decline against placebo was 0.4 points on the 18-point CDR-SB scale.

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[32] *Comment of the American Academy of Neurology to aducanumab Advisory Committee* available for download at https://www.regulations.gov/comment/FDA-2018-N-0410-0029

[33] Defendant Vounatsos told investors at the January 14, 2020 JP Morgan Healthcare Conference that "[t]here is a clear bottleneck in diagnosis capacity."

342. Aducanumab's approval imposes other costs. It will at a minimum slow recruitment for clinical trials of other Alzheimer's Disease treatments. Sponsors will have to convince patients to forego aducanumab, an FDA-approved treatment, in favor of a clinical trial where they would receive either an untried treatment or a placebo. Further, later treatments will have to show they are at least as effective as aducanumab. Aducanumab's results varied both in toto and by subgroup between all of its clinical trials. Even if Biogen's evidence for aducanumab's efficacy were sufficient, the evidence would not show how effective aducanumab is and for which patients. Companies trying to bring effective drugs to market may not be able to show non-inferiority to aducanumab because of the morass of its clinical trial results.

343. Aducanumab's approval also leaves biotech companies with perverse incentives. Biotech companies can put hundreds of millions of dollars at risk developing novel Alzheimer's therapies and putting them through clinical trials. Or they can earn billions of dollars by developing pointless products like aducanumab that reduce amyloid plaque without benefiting patients.

344. This danger is not just theoretical. On July 30, 2021, AbbVie announced that it would advance a drug targeting amyloid beta into clinical trials and shelve Phase II trials for another drug targeting tau.

IX. ADDITIONAL FACTS FURTHER PROBATIVE OF SCIENTER

i. "We have nothing to hide"

345. When Biogen presents clinical trial results, it usually provides much more information than it did when it announced aducanumab Phase III results.

346. Defendants themselves acknowledged that the Phase III results they presented were less thorough than usual. For example, in the December 5, 2019 Q&A, an analyst commented that:

> **Q:** I have one for [Sandrock] and one for [Budd-Haeberlein], if I may. [Sandrock]***, I've tracked so many of your data presentations over the years. And I felt like today, it seemed like there was so much presented but also so much not presented perhaps. And I couldn't tell why.*** So could you speak to what the carrier and noncarriers look like***? And should we assume that vast majority of the patients and the patients that had "sufficient exposure" were noncarriers?*** That was one for you, [Sandrock].
>
> And [Budd-Haeberlein], from your perspective, it seemed like everything we're looking at is a function of 2 things: one is the real data, which is the completers; and one is assumed data, which is the noncompleters. So from your perspective, how – like what was the thought process in getting comfortable assuming that the effect size in noncompleters should mirror the effect size in completers? And is there regulatory feedback and/or sensitivity analyses that support that?
>
> **Defendant Sandrock:** So I guess I'll start with the first question. And [analyst], I mean, look, as we said at the very beginning of this call, we're not presenting any data that we didn't already present this morning. ***And you're right, I mean, typically, we do present a lot of things, subgroups included, in the past. You're right, we did do that. There's a time and a place for everything.*** And look, this will soon be under review at regulatory authorities. And so for that reason, we're very sensitive about what we want to present now. ***We have nothing to hide.*** But there's a time and a place for everything. And in due time, I look forward to presenting all the data that make it important for – so that physicians can make the very best benefit/risk decisions if the drug becomes approved.
>
> **Defendant Budd-Haeberlein:** Yes. Thanks, [Sandrock]. I'll just add a comment to that. I'm not sure if I was clear this morning. And that is that the ApoE4 carrier status was well balanced over the arms of each study, was similar in both studies. And this is in the ITT population. But also in that Protocol Version 4 population, ApoE4 carriage was balanced. And that was why we used that particular methodology or one of the reasons. ***So while subgroups are really important***, there's a time and place for us to disclose much more data. I ***think everybody is looking to hear that we have that balance in the studies.***
>
> [Analyst], to your comment on real data completers versus noncompleters, the analysis method and the data set that we use. So the ITT and the MMRM are in fact the preferred method, as outlined in regulatory guidance on Alzheimer's disease therapeutics. And that was our primary statistical analysis. And so having a prespecified primary statistical analysis plan is what we – one would want to apply when a data set first comes in. However, as we've discussed, given that we had differences between the studies, we went further to do sensitivity analyses, including looking at the completers, to ensure that it

> wasn't an aspect of early termination that was making the data look the way it was. And as we showed in October, both the ITT and the OTC data sets are equivalent.

347. Indeed, when Biogen presented the Study 103 results, it made the raw data available to researchers.

348. Defendants knew revealing the data would show their explanation for Study 301's failure was false. So they made the out-of-character decision to withhold data with aducanumab's Phase III results.

ii. Defendants Told Investors They Had Taken Exceptional Care In Reviewing and Analyzing the Aducanumab Phase III Clinical Trial Data

349. In response to analyst questions, Defendant Sandrock stated:

> We don't file [for FDA approval] willy-nilly. I mean we only go to filing when we believe that there's a benefit/risk argument based on science, based on data. And look, I mean, if you look at our history, we haven't done filings right and left without good reason. And so – and look, it's a lot of work to do a filing. And it's also a lot of work for FDA or other regulators that have to review a filing. So these are not things that we just do lightly.

PLAINTIFFS' CLASS ACTION ALLEGATIONS

350. Plaintiffs bring this action as a class action pursuant to Federal Rule of Civil Procedure 23(a) and (b)(3) on behalf of a Class, consisting of all those who purchased or otherwise acquired the publicly traded securities of Biogen during the Class Period (the "Class"); and were damaged upon the revelation of the alleged corrective disclosures. Excluded from the Class are Defendants herein, Biogen's officers and directors, at all relevant times, members of their immediate families and their legal representatives, heirs, successors or assigns and any entity in which Defendants have or had a controlling interest.

351. The members of the Class are so numerous that joinder of all members is impracticable. Throughout the Class Period, the Company's securities were actively traded on NASDAQ. While the exact number of Class members is unknown to Plaintiffs at this time and

can be ascertained only through appropriate discovery, Plaintiffs believe that there are hundreds or thousands of members in the proposed Class. Record owners and other members of the Class may be identified from records maintained by Biogen or its transfer agent and may be notified of the pendency of this action by mail, using the form of notice similar to that customarily used in securities class actions.

352. Plaintiffs' claims are typical of the claims of the members of the Class as all members of the Class are similarly affected by Defendants' wrongful conduct in violation of federal law that is complained of herein.

353. Plaintiffs will fairly and adequately protect the interests of the members of the Class and have retained counsel competent and experienced in class and securities litigation. Plaintiffs have no interests antagonistic to or in conflict with those of the Class.

354. Common questions of law and fact exist as to all members of the Class and predominate over any questions solely affecting individual members of the Class. Among the questions of law and fact common to the Class are:

(a) whether Defendants' acts as alleged violated the federal securities laws;

(b) whether Defendants' statements to the investing public during the Class Period misrepresented material facts about the financial condition, business, operations, and management of Biogen;

(c) whether Defendants' statements to the investing public during the Class Period omitted material facts necessary to make the statements made, in light of the circumstances under which they were made, not misleading;

(d) whether the Individual Defendants caused Biogen to issue false and misleading SEC filings and public statements during the Class Period;

(e) whether Defendants acted knowingly or recklessly in issuing false and misleading SEC filings and public statements during the Class Period;

(f) whether the prices of Biogen's securities during the Class Period were artificially inflated because of the Defendants' conduct complained of herein; and

(g) whether the members of the Class have sustained damages and, if so, what is the proper measure of damages.

355. Common questions of law and fact predominate over any questions affecting only individual Class members. Because the common stock of Biogen traded in an efficient market and Defendants' false and misleading statements had impacted the price of Biogen common stock, Plaintiffs will establish reliance for himself and the Class through the fraud-on-the-market doctrine in that:

(a) Defendants made public misrepresentations or failed to disclose material facts during the Class Period;

(b) the omissions and misrepresentations were material;

(c) the Company's securities are traded in an efficient market;

(d) the Company's securities were liquid and traded with moderate to heavy volume during the Class Period;

(e) the Company traded on the NASDAQ, and was covered by many analysts;

(f) the misrepresentations and omissions alleged would tend to induce a reasonable investor to misjudge the value of the Company's securities; Plaintiffs and members of the Class purchased and/or sold the Company's securities between the time the Defendants failed to disclose or misrepresented material facts and the time the true facts were disclosed, without knowledge of the omitted or misrepresented facts; and

(g) Unexpected material news about the Company was rapidly reflected in and incorporated into the Company's stock price during the Class Period.

356. Based upon the foregoing, Plaintiffs and the members of the Class are entitled to a presumption of reliance upon the integrity of the market, establishing predominance.

357. Alternatively, Plaintiffs and the members of the Class are entitled to the presumption of reliance established by the Supreme Court in *Affiliated Ute Citizens of Utah v. United States*, 406 U.S. 128, 92 S. Ct. 1456, 31 L. Ed. 2d 741 (1972), as Defendants omitted material information in their Class Period statements in violation of a duty to disclose such information, as detailed above.

358. A class action is superior to all other available methods for the fair and efficient adjudication of this controversy since joinder of all members is impracticable. Furthermore, as the damages suffered by individual Class members may be relatively small, the expense and burden of individual litigation make it impossible for members of the Class to individually redress the wrongs done to them. There will be no difficulty in the management of this action as a class action.

NO SAFE HARBOR

359. The statutory safe harbor provided for forward-looking statements under certain circumstances does not apply to any of the allegedly false statements pleaded in this Complaint. The statements alleged to be false and misleading herein all relate to then-existing facts and conditions. In addition, to the extent certain of the statements alleged to be false may be characterized as forward looking, they were not identified as "forward-looking statements" when made and there were no meaningful cautionary statements identifying important factors that could cause actual results to differ materially from those in the purportedly forward-looking statements.

COUNT I

Violation of Section 10(b) of The Exchange Act and Rule 10b-5

Against All Defendants

360. Plaintiffs repeat and reallege each and every allegation contained above as if fully set forth herein.

361. Plaintiffs assert this claim against all Defendants, basing the claim upon Section 10(b) of the Exchange Act, 15 U.S.C. § 78j(b), and Rule 10b-5 promulgated thereunder by the SEC.

362. During the Class Period, in violation of Section 10(b) of the Exchange Act and Rule 10b-5(b), the Company and the Individual Defendants, individually and in concert, directly or indirectly, disseminated or approved the false statements specified above, which they knew or deliberately disregarded were misleading in that they contained misrepresentations, omitted material facts, and failed to disclose material facts necessary to make the statements made, in light of the circumstances under which they were made, not misleading.

363. The Company and the Individual Defendants violated §10(b) of the 1934 Act and Rule 10b-5(a) and (c) in that they employed devices, schemes and artifices to defraud and/or engaged in acts, practices and a course of business that operated as a fraud or deceit upon Plaintiffs and others similarly situated in connection with their purchases of Biogen's securities and directly impacted the price of Biogen's common stock during the Class Period.

364. The Company and the Individual Defendants acted with scienter in that they knew or recklessly disregarded that the public documents and statements issued or disseminated in Biogen's name were materially false and misleading and omitted material information; knew or recklessly disregarded that such statements or documents would be issued or disseminated to the

investing public; and knowingly or recklessly and substantially participated or acquiesced in the issuance or dissemination of such statements or documents as primary violations of the securities laws. These Defendants, by virtue of their receipt of information reflecting the true facts of the Company, their control over, and/or receipt and/or modification of the Company's allegedly materially misleading statements or material omissions, and/or their associations with the Company which made them privy to confidential proprietary information concerning the Company, participated in the fraudulent scheme alleged herein. Information showing that Biogen, by and through the Individual Defendants, and other senior Biogen officers and employees, acted knowingly or with reckless disregard for the truth is peculiarly within Defendants' knowledge and control.

365. The Individual Defendants knew or recklessly disregarded the material omissions and/or the falsity of the material statements set forth above, and intended to deceive Plaintiffs and the other members of the Class, or, in the alternative, acted with reckless disregard for the truth when they failed to ascertain and disclose the true facts in the statements made by them or other Biogen personnel to members of the investing public, including Plaintiffs and the Class.

366. As a direct and proximate result of the scheme or artifice to defraud that lead directly to Biogen's disclosing materially false and misleading information, the market price of Biogen's securities was artificially inflated during the Class Period. In ignorance of the falsity of the statements at issue, Plaintiffs and the other members of the Class relied on the statements described above and/or on the integrity of the market price of Biogen's securities during the Class Period in purchasing the Company's securities at prices that were artificially inflated as a result of Biogen's false and misleading statements and omissions.

367. Had Plaintiffs and the other members of the Class been aware that the market price of Biogen's securities had been artificially and falsely inflated by the fraudulent scheme that caused Biogen to issue misleading financial statements, and by the material adverse information which the Company did not disclose, causing artificial inflation in Biogen's stock price, they would not have purchased Biogen's securities at the artificially inflated prices that they did, or at all.

368. As a result of the wrongful conduct alleged herein, Plaintiffs and other members of the Class have suffered damages in an amount to be established at trial.

369. By reason of the foregoing, Defendants Biogen and the Individual Defendants have violated Section 10(b) of the Exchange Act and Rule 10b-5 promulgated thereunder and are liable to the Plaintiffs and the other members of the Class for substantial damages which they suffered in connection with their purchases of Biogen's securities during the Class Period.

COUNT II

Violation of Section 20(a) of the Exchange Act

Against the Individual Defendants

370. Plaintiffs repeat and reallege each and every allegation contained in the foregoing paragraphs as if fully set forth herein.

371. During the Class Period, Biogen, by and through its officers and directors, violated Section 10(b) of the Exchange Act and SEC Rule 10b-5 promulgated thereunder.

372. The Individual Defendants participated in the operation and management of Biogen and its operating units, and conducted and participated, directly and indirectly, in the conduct of Biogen's business affairs. As officers and/or directors of a publicly owned company, the Individual Defendants had a duty to disseminate accurate and truthful information with respect

to Biogen's financial condition and results of operations, and to correct promptly any public statements issued by Biogen which had become materially false or misleading.

373. Because of their positions of control and authority as senior officers, the Individual Defendants were able to, and did, control the contents of the various reports, press releases and public filings which Biogen disseminated in the marketplace during the Class Period. Throughout the Class Period, the Individual Defendants exercised their power and authority over Biogen. The Individual Defendants, therefore, were "controlling persons" of Biogen within the meaning of Section 20(a) of the Exchange Act. In this capacity, they participated in the unlawful conduct alleged which artificially inflated the market price of Biogen's securities.

374. Each of the Individual Defendants, therefore, acted as a controlling person of Biogen. By reason of their senior management positions and/or being directors of Biogen, each of the Individual Defendants had the power to direct the actions of, and exercised the same, to cause Biogen to engage in the unlawful acts and conduct complained of herein. Each of the Individual Defendants exercised control over the general operations of Biogen and possessed the power to control the specific activities which comprise the primary violations about which Plaintiffs and the other members of the Class complain.

375. By reason of the foregoing, the Individual Defendants have violated Section 20(a) of the Exchange Act and are jointly and severally liable to the Plaintiffs and the other members of the Class for substantial damages that they suffered in connection with their purchases of Biogen's securities during the Class Period.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs demand judgment against Defendants as follows:

A. Determining that the instant action may be maintained as a class action under Rule 23 of the Federal Rules of Civil Procedure, certifying Plaintiff as Class representative, and approving Lead Counsel and Local Counsel as counsel to the Class;

B. Requiring Defendants to pay damages sustained by Plaintiffs and the Class by reason of the acts and transactions alleged herein;

C. Awarding Plaintiffs and the other members of the Class pre-judgment and post-judgment interest, as well as their reasonable attorneys' fees, expert fees and other costs; and

D. Awarding such other and further relief as this Court may deem just and proper.

DEMAND FOR TRIAL BY JURY

Plaintiffs hereby demand a trial by jury.

Dated: August 4, 2021

Respectfully submitted,

THE ROSEN LAW FIRM, P.A.

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CERTIFICATE OF SERVICE

I hereby certify that on August 4, 2021, a true and correct copy of the foregoing **SECOND AMENDED CLASS ACTION COMPLAINT FOR VIOLATIONS OF THE FEDERAL SECURITIES LAWS** was served by CM/ECF to the parties registered to the Court's CM/ECF system.

/s/Laurence Rosen